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Association of neutrophil-lymphocyte ratio (NLR) with the anthracycline-based neoadjuvant chemotherapy (NAC) clinical response in locally advanced breast cancer (LABC) in young women

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ABSTRACT

Background: Breast cancer in young women is one of the leading causes of cancer death in young women worldwide, including in Indonesia. Most patients come to the hospital at the advanced stage. Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer. However, half of breast cancer patients had a negative response to therapy.
Methods: A retrospective cohort, analytic observational study to determine the association between NLR and anthracycline-based NAC clinical response in locally advanced young age breast cancer in Dr. Soetomo General Hospital, Surabaya.
Results: We analyze a total of 44 patients. 81.8% had stage IIIB, 93.2% >50 mm tumor size. Most of the cases had invasive ductal carcinoma type (86.4%), grade 3 (52.3%), and Luminal B HER2-negative type (34.1%). 52.3% of patients had a negative clinical response. The mean NLR was 3.07 ± 1.69, with a cut-off value of 2.805. There was no significant association between age, tumor size, histopathological type, grade, and subtype with neoadjuvant chemotherapy clinical response. There was a significant relationship between NLR with anthracycline-based NAC clinical response in locally advanced young age breast cancer ($p < 0.001$).
Conclusion: There was a significant relationship between NLR with the anthracycline-based neoadjuvant chemotherapy clinical response in young women with LABC.

Keywords: *breast cancer, clinical response, neoadjuvant chemotherapy, neutrophil-lymphocyte ratio, young age.*
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INTRODUCTION

Breast cancer at a young age is the most common cancer in young women and has been the leading cause of cancer death in young women worldwide, including in Indonesia. According to World Health Organization (WHO), 247,784 new cases of breast cancer were detected in women ages 15-39 years in 2020. In Indonesia, 9,701 young women were diagnosed with breast cancer, and 1,635 patients died of breast cancer (20.5% death of all cancer in women ages 15-39 years old).[1] Young age breast cancer generally presents with a higher stage, more aggressive characteristics, and higher recurrence and mortality rate; therefore, it needs a different therapeutic strategy.[2] Anwar *et al*. reported an 11.4% incidence rate of early onset breast cancer in Yogyakarta, in which 64% of them came to the hospital at an advanced stage.[3]

The management of LABC at a young age is principally similar to LABC in general. Multimodality therapy, which consists of systemic chemotherapy and locoregional therapy, is the treatment option for LABC, with NAC as the standard treatment. Anthracycline-based chemotherapy is recommended for LABC.[4–6] Pathological complete response (pCR) after neoadjuvant chemotherapy is significantly related to prolonged disease-free survival (DFS) and overall survival (OS) in LABC.[5] Breast cancer at a young age tended to have a worse prognosis partly due to more aggressive tumor characteristics, but their response to chemotherapy seems to be better. Patients who do not respond well to NAC will experience a delay in the selection of another treatment modality. Therefore, it is important to investigate the predictive factor of NAC clinical response so that we can prevent the administration of unnecessary chemotherapy. There are several predictive factors for NAC chemotherapy response, such as age, tumor size, histopathologic type, histologic grade, hormone receptor status (estrogen receptor/ ER and progesterone receptor/ PR), and proliferative factor (HER2/neu, Ki-67), and inflammatory markers.[7,8] Current studies showed no consistent results on the significance of these factors

in NAC response in breast cancer at a young age.[6]

The immune system has a pivotal role in breast cancer response to chemotherapy.[9] Neutrophils are generally considered a pro-tumor factor in several tumor types and are known to promote cancer cell proliferation, angiogenesis, and metastasis through multiple mechanisms, while lymphocytes play a role in anti-tumor immune reaction. High neutrophil infiltration is related to cancer aggressiveness and therapeutic resistance. Thus, the neutrophil-to-lymphocyte ratio (NLR) may be related to chemosensitivity. Several studies showed that the higher NLR indicates higher resistance to chemotherapy drugs, and low NLR may indicate a favorable outcome after anthracycline-based NAC in triple-negative breast cancer (TNBC).[10–12]

To date, there has been no study on the relationship between NLR and NAC response in young age LABC patients in Indonesia. NLR examinations are easy to do, widely available, and routinely performed prior to the chemotherapy session. This study aimed to analyze the association between NLR and anthracycline-based NAC in young age LABC patients.

METHODS

Study design and participants

This is a retrospective cohort study conducted at Dr. Soetomo General Hospital (Surabaya, Indonesia). In this study, we included patients < 40 years with LABC, received anthracycline-based neoadjuvant chemotherapy, and had no history of chemotherapy or radiotherapy. We excluded patients with no complete data in the medical record and patients with chronic autoimmune disease. We used a total sampling method and included all patients who fulfilled the inclusion criteria. In total, we retrospectively reviewed 44 medical records of females aged less than 40 years old with LABC who received anthracycline-based neoadjuvant chemotherapy between 2015 and 2020.

This study was reviewed and approved by the Medical Ethical Committee of dr. Soetomo General Hospital Surabaya (approval number 0427/LOE/301.4.2/IV/2021) follows the guidelines of the Declaration of Helsinki.

Breast cancer diagnosis, neoadjuvant chemotherapy regimen, and clinical response

Breast cancer was confirmed histologically by fine needle aspiration biopsy, core needle biopsy, or incisional biopsy. We also classified the breast cancer subtypes using immunohistochemistry by examining the expression of estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and Ki67. Tumor stage, T and N factors were stratified based on the American Joint Committee on Cancer (AJCC) 2018.

All patients received a standardized protocol of anthracycline-based neoadjuvant chemotherapy consisting of FEC (500 mg/m^2 fluorouracil, 100 mg/m^2 epirubicin, and 500 mg/m^2 cyclophosphamide) or FAC (500 mg/m^2 fluorouracil, 50 mg/m^2 doxorubicin, and 500 mg/m^2 cyclophosphamide). Peripheral blood was obtained 1-7 days before NAC administration. The numbers of white blood cells were determined using a Dimensional Chemistry System, Siemens (USA) hematology analyzer, which is calibrated every 28 days.

We used the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria to assess the patients' post-chemotherapy clinical response and divided them into four categories: complete response, partial response, stable disease, and progressive disease.[13] In this study, positive clinical response was defined as patients who had a complete or partial response, and negative clinical response was classified as patients who had stable or progressive disease.

Data collection

We reviewed medical records, laboratory findings, histopathology findings, and radiology findings for all 44 patients who met the criteria. All the data were obtained from paper-based medical records and electronic medical records. Information collected includes the patient's name, medical record number, age, date of birth, patient's history, physical examination, date of breast cancer diagnosis, pre-treatment tumor size, tumor stage at the time of the first admission, histopathology type, histopathology grade, tumor subtype (ER status, PR status, HER2/neu status, and Ki67), pre-treatment white blood cells count, chemotherapy regimen and date of administration, post-chemotherapy tumor size, and clinical response towards chemotherapy.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software package version 24.0 (IBM Corp., Armonk, NY, USA). The variables were analyzed and presented as frequency distribution and cross-tabulation. We examined the associations between NLR and clinical chemotherapy response using Chi-squared (χ^2) test. Receiver operating characteristic (ROC) curve analysis was performed to calculate an optimal cut-off value for NLR to predict the clinical response after chemotherapy. A P value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

There were 44 patients with locally advanced young age breast cancer who received anthracycline-based neoadjuvant chemotherapy in the Surgical Oncology outpatient clinic, Dr. Soetomo General Hospital Surabaya, between 2015-2020 that met the inclusion and exclusion criteria. The mean age was 34.41 ± 4.5 years, with the youngest being 22 years old. Most of the patient came in stage 3B (36/44; 81.8%), with tumor size > 50 mm (41/44; 93.2%). Approximately half of the tumors (52.3%) were high-grade tumors, and 34.1% were luminal B HER2-subtype. Patient characteristics are shown in Table 1.

NLR and clinical response towards chemotherapy

We used ROC analysis to calculate the optimal cut-off value to predict the clinical response to chemotherapy. We found that the optimal cut-off value was 2.805 (AUC= 0.837; 95% CI = 0.709 – 0.966). Then, we classified the NLR value into high-NLR (≥ 2.805) and low-NLR (< 2.805) based on the cut-off value determined by ROC curve analysis. We found that 52.3% of patients had a negative neoadjuvant chemotherapy response (stable disease or progressive disease), and 48.7% of

patients had a positive response (complete pathological response or partial response). The sensitivity, specificity, PPV, NPV, and accuracy of NLR to predict the clinical response was 85.7%, 82.6%, 81.8%, 86.4%, and 84.1%, respectively. The ROC curve is shown in Figure 1.

Association between patient characteristics and NLR

The association between confounding variables (age, pre-treatment tumor size, presence of ulceration, body mass index (BMI), histopathology grade, and tumor subtype) and NLR were analyzed and presented in Table 2. We found that there was no significant association between age, tumor size, ulceration, body mass index, histopathology grade, and breast cancer subtypes with the NLR value (P > 0.05 for all).

Association between patient characteristics and clinical chemotherapy response

The association between confounding variables (age, pre-treatment tumor size, histopathology type, histopathology grade, and tumor subtype) and clinical chemotherapy response were analyzed (Table 3). There were no significant association between age, tumor size, ulceration, body mass index, histopathology grade, and breast cancer subtypes with the clinical response to chemotherapy (P > 0.05 for all).

Table 1. Patient characteristics.

Parameters	n	Percentage
Total patients	44	
Age		
< 35 years	25	56.8%
35-39 years	19	43.2%
Tumor size		
≤ 50 mm	3	6.8%
> 50 mm	41	93.2%
Stage		
2B	2	4.5%
3A	4	9.1%
3B	36	81.8%
3C	2	4.5%
Histopathology type		
Ductal carcinoma	38	86.4%
Non-ductal carcinoma	6	13.6%
Histopathology grade		
DCIS	1	2.3%
1	5	11.4%
2	15	34.1%
3	23	52.3%
Tumor subtype		
Luminal A	2	4.5%
Luminal B HER2-	15	34.1%
Luminal B HER2+	10	22.7%
HER2 overexpression	8	18.2%
TNBC	9	20.5%
NLR		
Low	22	50%
High	22	50%
Clinical chemotherapy response		
Complete response	1	2.3%
Partial response	20	45.5%
Stable disease	18	40.9%
Progressive disease	5	11.4%
Clinical response conclusion		
Positive response	21	47.7%
Negative response	23	52.4%

Association between NLR and clinical chemotherapy response

We analyzed the association between NLR with the clinical response after anthracycline-based chemotherapy (Table 4). We found that in a group with a low NLR value, there were 18 patients (18/22; 81.8%) with positive clinical responses and 4 patients (4/22; 18.2%) with negative clinical responses. In the group with a high NLR value, we found that there were 3 patients with positive clinical responses and 19 patients (86.4%) with negative clinical responses. There was a statistically significant association between NLR and clinical chemotherapy response (P < 0.001).

DISCUSSION

Breast cancer is the most common cancer in young women and has been the leading cause of cancer death in young women worldwide and also in Indonesia. Breast cancer at a young age, defined as breast cancer that was diagnosed before 40 years of age, is known to have different characteristics than breast cancer occurring later in life. It is associated with more aggressive characteristics, higher recurrence and mortality rate. In Dr. Soetomo General Hospital, there were 92 cases of young age breast cancer between 2012-2013. 41.3% of the patient came from advanced breast cancer, 36.9% from locally advanced breast cancer, and 21.8% came from early breast cancer.[14]

From January 2015 – October 2020, there were 44 patients with young age breast cancer who received anthracycline-based neoadjuvant chemotherapy. This number showed that the prevalence of LABC at a young age is considerably low. However, the biggest problem was that the LABC in young patients was often detected in a later stage when the mass was considered a larger size and with aggressive characteristics.[6] Young age breast cancer patients are often diagnosed at an advanced stage, probably caused by

several factors, such as less awareness of breast cancer due to the young age and the lower sensitivity of mammography due to the higher density of breast tissue in younger women.[2] In addition, doctors are usually less likely to suspect malignancy at a young age patient, making it a pitfall for breast cancer diagnosis from a medical professional's point of view.

Based on histopathological findings, the majority in this study showed ductal carcinoma (86.4%) with a high tumor grade (52.3%). These results are the same as several other studies which state that invasive ductal carcinoma is the most common type found in young breast cancer, which is 85% to 90% of the total cases.[15] In this study, most of the patient was luminal B HER2-negative subtype (34.1%), followed by luminal B HER2-positive (22.7%), TNBC (20.5%), HER2-overexpression (18.2%), and luminal A (4.5%). Several studies have found different characteristics of young age breast cancer. Younger onset is associated with more aggressive cancers, such as TNBC and Her2-type. The majority of young breast cancer subtypes found were TNBC (30.8% of cases), followed by Luminal B, Her2/neu type and luminal A (6). Higher TNBC proportion in the younger patient might be associated with the higher BRCA1 mutation, luminal progenitor, dan *c-kit*.[2]

LABC in young age management is basically similar to LABC treatment strategy in general. Combined multimodality therapy consists of systemic chemotherapy, and locoregional therapy has been the mainstay of treatment. Neoadjuvant chemotherapy is the standard treatment of LABC, and it is recommended to use an anthracycline-based regimen with a target to achieve a complete pathological response (pCR) so that disease-free survival (DFS) and overall survival (OS) can be prolonged (4–6). In a 5 years cohort study, breast cancer patient who achieved pCR had better DFS (73.4% vs. 46.1%, P = 0.032), and OS (82.5% vs 56.4%, P = 0.022).[16]

There are several predictive factors for NAC chemotherapy response, such as age, tumor size, histopathologic type, histologic grade, hormone receptor status (ER and PR), proliferative factor (HER2/neu and Ki-67), and inflammatory markers.[7,8] Current studies showed no consistent results on the role of these factors in NAC response in young age breast cancer.[6] In this study, there was no significant association between confounding variables (age, tumor size, tumor type, tumor grade, and tumor subtype) with anthracycline-based neoadjuvant chemotherapy response in locally advanced young age breast cancer.

NLR has become a concern to many researchers. Several studies showed that the higher NLR indicates higher resistance to chemotherapy drugs, and low NLR may indicate a favorable outcome after anthracycline-based NAC in triple-negative breast cancer (TNBC).[10–12] In this study, the majority of the subjects had high NLR with negative clinical responses. We found that there was a significant relationship between NLR with anthracycline-based neoadjuvant chemotherapy clinical response in early onset LABC. Therefore, we can consider the use of NLR to predict the outcome of NAC in a breast cancer patient. Importantly, the variables used to calculate the NLR are always available in every patient due to the requirement of performing a complete blood count in every patient. The use of NLR might be very useful, especially in underdeveloped and developing countries, where the cost efficiency of healthcare services is necessary.

There are controversies about the relationship between breast cancer subtypes and response to chemotherapy and which subtypes are most responsive to chemotherapy. Several studies reported that TNBC and HER2-positive patients achieved the most positive neoadjuvant chemotherapy response.[17–19] Meanwhile, from a study in Serbia that analyzed the effect of locally advanced breast cancer subtypes on the response to anthracycline-based chemotherapy, it was found that pCR was highest in non-luminal/HER2-positive patients and lowest in luminal HER2-negative.[20] A study in Bali in 2012

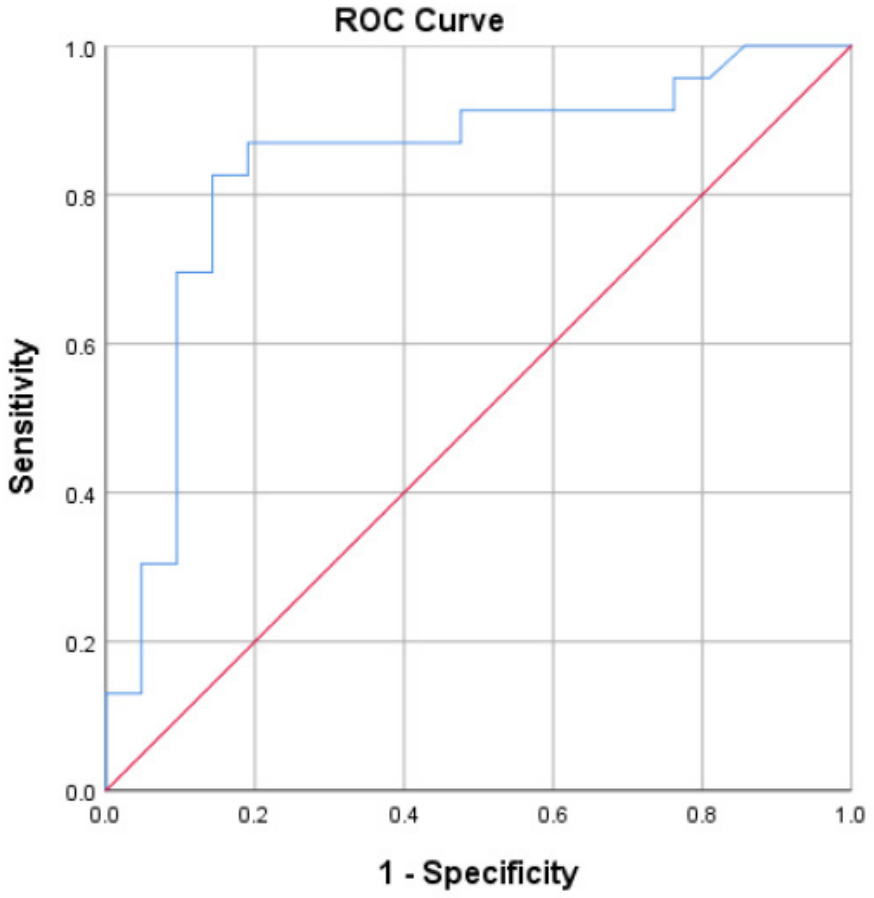

Figure 1. ROC analysis of NLR value.

reported that the most positive response to neoadjuvant chemotherapy was found in the HER2+ group and the least in the TNBC subtype.[21] In this study, the majority of young women with LABC were found with the Luminal B HER2- subtype, and 60% of them experienced a positive chemotherapy response. This is in accordance with the National Cancer Database study, which showed that 80.5% of patients with HR+/HER2- who received neoadjuvant chemotherapy had a positive clinical response (complete response or partial response), and underwent more mastectomy than TNBC and HER2+ subtypes.[22] This result is different from several previous studies and might be due to other factors that also affect the response to chemotherapy, such as the genetic profile of breast cancer itself. There are some differences in somatic mutations in young patients compared to older patients. At a young age in breast cancer, the prevalence of TP53, PIK3CA, GATA3, and CTNNB1 mutations is higher.[23] A 2012 meta-analysis study concluded that TP53 status is a predictive factor for neoadjuvant chemotherapy response in breast cancer patients, whereas TP53 overexpression and/or TP53 gene mutation are associated with better chemotherapy response.[24] Breast cancer patients with positive GATA3 expression showed luminal differentiation with high estrogen receptor expression and could be used as a predictor of poor response to chemotherapy.[25] Various studies have shown that the genetic profile of breast cancer can influence the response to neoadjuvant chemotherapy. A high 21-gene breast recurrence score in young breast cancer patients with ER-positive/HER2-negative is associated with an increased likelihood of achieving pCR following neoadjuvant chemotherapy. Examination of the genetic profile of breast cancer before chemotherapy can assist in the selection of therapy in young breast cancer patients who require neoadjuvant therapy.[26]

Table 2. Association between patient characteristics and NLR.

Variables	NLR Value		P value
	Low NLR	High NLR	
Age			
< 35 years	10 (52.6%)	9 (47.4%)	0.761
35 – 39 years	12 (48%)	13 (52%)	
Tumor size			
≤ 50 mm	1 (33.3%)	2 (66.7%)	0.550
> 50 mm	21 (51.2%)	20 (48.8%)	
Ulceration			
Yes	9 (39.1%)	14 (60.9%)	0.131
No	13 (61.9%)	8 (38.1%)	
Body mass index			
Underweight	1 (16.7%)	5 (83.3%)	0.283
Normal	7 (50%)	7 (50%)	
Overweight	9 (64.3%)	5 (35.7%)	
Obesity	5 (50%)	5 (50%)	
Histopathology grade			
DCIS	0 (0%)	1 (100%)	0.354
1	4 (80%)	1 (20%)	
2	8 (53.3%)	7 (46.7%)	
3	10 (43.5%)	13 (56.5%)	
Tumor subtype			
Luminal A	1 (50%)	1 (50%)	0.136
Luminal B Her2-negative	9 (60%)	6 (40%)	
Luminal B Her2-positive	7 (63.6%)	4 (36.7%)	
Her2 overexpression	4 (57.1%)	3 (23.9%)	
TNBC	1 (11.1%)	8 (88.9%)	

***DCIS: ductal carcinoma in situ; TNBC: triple-negative breast cancer**

The immune system has a pivotal role in breast cancer response to chemotherapy.[9] High neutrophils produce various cytokines and chemokines, including oncostatin, which causes increased angiogenesis. NE and cathepsin G, which increases proliferation and angiogenesis, and arginase 1, which causes immunosuppression.[12] High neutrophils also play a role in doxorubicin resistance through several pathways. First, neutrophils release IL-6, which can activate the JAK pathway, resulting in doxorubicin efflux from cells. The classic IL-6/JAK/STAT3 pathway can induce chemotherapy resistance in breast cancer. Doxorubicin resistance occurs via the HIF-1 pathway.[27] This is involved in the epithelial-to-mesenchymal transition (EMT) process.[28] Hypoxia can lead to amplification of gene expression associated with drug efflux and induction of angiogenesis.[29] Neutrophils release TNF-α, which induces doxorubicin resistance in breast cancer via reverse signaling.[30] Third, neutrophils release IL-1ß, which upregulates BIRC3, an inhibitor of apoptosis.[31] Lymphocytes produce antibodies, kill viruses and tumor cells, and regulate immune responses. Tumor-infiltrating lymphocytes (TILs) in breast cancer are associated with achieving pCR after neoadjuvant chemotherapy.[9] TILs plays an important role in mediating chemotherapy response and promotes good clinical outcome in all subtypes of breast cancer.[32] CD4+ T-helper 1 (Th1) facilitates antigen presentation through cytokine secretion and APC activation. CD8+ cytotoxic T-cells (CTL) are required for tumor destruction.[33]

There are limitations to this study. First, the number of samples in this study is relatively small. However, this number represents the low prevalence of LABC in young women. Second, this study was conducted in one tertiary hospital in Surabaya; therefore, this study might not be sufficient to represent Indonesia as a whole. A further nationwide study

conducted in several locations in Indonesia might be important to provide more detailed data on the LABC at a young age in Indonesia.

CONCLUSION

There was a significant relationship between NLR with anthracycline-based neoadjuvant chemotherapy clinical response in young women with LABC.

CONFLICT OF INTEREST

No competing interests were declared.

AUTHOR CONTRIBUTION

Conceived the study: VIW. Designed the study: VIW, VVCMT, and IA. Analyzed the data: VIW, VVCMT, and IA. Wrote the manuscript: VIW and VVCMT. Review the manuscript: VVCMT and IA.

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Table 3. Association between patient characteristics and clinical chemotherapy response.

Variables	Clinical chemotherapy response		P value
	Positive	Negative	
Age			
< 35 tahun	11 (57.9%)	8 (42.1%)	0.239
35 – 39 tahun	10 (40%)	15 (60%)	
Tumor size			
≤ 50 mm	1 (33.3%)	2 (66.7%)	0.605
> 50 mm	20 (48.8%)	21 (51.2%)	
Histopathology type			
Ductal carcinoma	16 (42.1%)	22 (57.9%)	0.06
Non-ductal carcinoma	5 (83.3%)	1 (16.7%)	
Histopathology grade			
DCIS	0 (0%)	1 (100%)	0.142
1	4 (80%)	1 (20%)	
2	9 (60%)	6 (40%)	
3	8 (34.8%)	15 (65.2%)	
Tumor subtype			
Luminal A	1 (50%)	1 (50%)	0.733
Luminal B Her2-	9 (60%)	6 (40%)	
Luminal B Her2+	5 (50%)	5 (50%)	
Her2 overexpression	3 (37.5%)	5 (62.5%)	
TNBC	3 (33.3%)	6 (66.7%)	

Table 4. Association between NLR and clinical chemotherapy response.

Parameters	Clinical response		P value
	Positive	Negative	
NLR			
Low (≤ 2.805)	18 (81.8%)	4 (18.2%)	<0.001
High (>2.805)	3 (13.6%)	19 (86.4%)	

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