Early changes of platelet-lymphocyte ratio correlate with neoadjuvant chemotherapy response and predict pathological complete response in breast cancer

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Abstract. Markers with inflammatory properties, such as the ratio of neutrophils to lymphocytes and the platelet-to-lymphocyte ratio (PLR), have been documented as potential indicators for predicting pathologic complete response (pCR) following neoadjuvant chemotherapy (NACT) in cases of breast cancer. However, whether early changes of PLR (ΔPLR) during NACT can predict pCR has not been reported. A total of 257 breast cancer patients who underwent NACT were retrospectively analyzed. PLR was calculated by evaluating the complete blood cell counts prior to NACT and following two cycles of NACT. The analysis focused on the association between changes in PLR and the response to chemotherapy, as well as the association with pCR. Patients who stayed in or changed to the low PLR level subgroup after two cycles of NACT exhibited a superior response to chemotherapy, in contrast to those who stayed in or changed to the high PLR level subgroup. Of the 257 patients, 75 (29.1%) achieved a pCR after NACT. In the multivariate analysis, there was a significant association between ΔPLR and pCR, whereas pre-treatment and post-treatment PLR did not show any significant association. In multivariate analysis, patients who had a ΔPLR <0 had a notably higher rate of pCR compared with patients with a ΔPLR ≥0. It was concluded that ΔPLR, rather than pre-treatment or post-treatment PLR, is associated with pCR. This suggested that the early changes of PLR after two cycles of NACT might serve as a more accurate predictor for chemotherapy response and pCR in breast cancer.

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Introduction

Breast cancer is currently the most frequently detected form of cancer and the primary contributor to cancer-related fatalities among women worldwide (1). Neoadjuvant chemotherapy (NACT) is extensively employed to enable surgery in locally advanced breast cancer or to reduce the size of the tumor, making breast-conserving surgery more achievable (2-4). NACT is further linked to the *in vivo* reaction of the tumor to chemotherapy, which can be directly assessed through clinical response (2).

It has been proposed that pathologic complete response (pCR) following NACT could be a good surrogate marker of disease free survival and overall survival, particularly in patients with more aggressive subtypes, such as triple-negative (TN) and human epidermal growth factor receptor 2 (HER2)-positive breast cancer (5-8). In addition, multiple studies have indicated that inflammatory markers, such as the ratio of neutrophils to lymphocytes (NLR) and the platelet-to-lymphocyte ratio (PLR) are also possibly associated of pCR in breast cancer following NACT (9-12). However, these studies mainly focused on baseline status of inflammatory markers before treatment and the clinical significance of the changes of inflammatory markers during or after treatment, which may reflect treatment response, is rarely studied.

Hence, the objective of the present study was to assess the potential of early changes of PLR (ΔPLR) observed prior to and following two cycles of NACT as predictive indicators for neoadjuvant chemotherapy response and pCR in breast cancer patients.

Materials and methods

Patients. This retrospective study analyzed the information of 257 individuals diagnosed with initial breast cancer at the

Chengdu Fifth People's Hospital (Sichuan, China) between June 2012 and July 2017. Baseline characteristics are given in Table I. Tumor staging, both clinically and pathologically, was determined based on the 8th edition of the Cancer Staging Manual by the American Joint Committee on Cancer (13). The project was approved by the Ethics Committee of Chengdu Fifth People's Hospital on January 13, 2022 (reference K2021-053-01). Due to the retrospective nature of this study and the utilization of solely anonymized clinicopathologic data, informed consent was not acquired.

To be eligible for the study, participants had to meet the following requirements: i) women aged 18-70 years; ii) clinical stage II or III; iii) diagnosed with primary breast cancer through core needle biopsy; iv) and having completed a minimum of six cycles of NACT. Exclusion criteria included patients who had been diagnosed with systemic inflammatory or chronic conditions, such as systemic lupus erythematous, liver cirrhosis, or end-stage renal disease prior to the surgery. Exclusion criteria also included patients who lacked data on pathological or laboratory findings, as well as those diagnosed with inflammatory breast carcinoma. In addition, neoadjuvant Trastuzumab was only administered to a small percentage of patients whose tumors were HER2-positive, because its high cost was not covered by medical insurance at that time. Consequently, those individuals were not included in our investigation.

NACT and response assessment. All patients in our facility at the Chengdu Fifth People's Hospital (Sichuan, China) were administered conventional chemotherapy treatments. Taxanes, anthracycline, and cyclophosphamide were the regimens most frequently used. Additional treatment plans consisted of EC (epirubicin and cyclophosphamide), FEC (fluorouracil, epirubicin and cyclophosphamide), CMF (fluorouracil, methotrexate and cyclophosphamide), and various combinations involving platinum compounds.

The clinical responses were evaluated every two cycles during the NACT treatment. Chemotherapeutic efficacy was assessed by categorizing tumor response into partial response (PR) and non-PR using the Response Evaluation Criteria in Solid Tumors (14). Following NACT, a pCR was determined by examining resected specimens under a microscope to confirm the absence of invasive tumor in both the breast and nodes. Patients with remaining ductal carcinoma *in situ* were also included in the pCR category (15).

Blood samples and definition. PLR is calculated by dividing the total number of platelets by the total number of lymphocytes. Pre-treatment PLR refers to the immediate performance of a routine blood test on patients diagnosed with breast cancer using peripheral vein blood. An additional blood test was conducted ~2 weeks following the completion of the second cycle of NACT. Therefore, the calculation of PLR alteration between prior to NACT and following two cycles of NACT was possible. The ΔPLR was determined by subtracting the pre-treatment PLR from the post-treatment PLR. In contrast to other studies, the present study employed PLR as an indicator of inflammation rather than NLR. Most patients received prophylactic granulocyte colony-stimulating factor during the NACT period, which will affect the growth and viability of neutrophils. Therefore, the study did not include NLR. In addition, there was no use of thrombocytopoiesis agents during the first two cycles of NACT.

Table I. Baseline characteristics of 257 patients.

Baseline characteristic	n=257
Median age, years (range)	50 (34-70)
Age group, n (%)	
<50 years	123 (47.9)
≥50 years	134 (52.1)
Menopausal status, n (%)	
Pre-menopausal	101 (39.3)
Post-menopausal	156 (60.7)
Histologic type, n (%)	
Invasive ductal carcinoma	234 (91.1)
Others	23 (8.9)
T Stage, n (%)	
cT 1-2	106 (41.2)
cT3-4	151 (58.8)
Nodal status, n (%)	
Positive	155 (60.3)
Negative	102 (39.7)
Grade, n (%)	
G1	116 (45.1)
G2	73 (28.4)
G3	68 (26.5)
Hormone receptor, n (%)	
Positive	153 (59.5)
Negative	104 (40.5)
HER2, n (%)	
Positive	60 (23.3)
Negative	197 (76.7)
Molecular subtype, n (%)	
Luminal A	113 (44.1)
Luminal B	24 (9.3)
Triple negative	60 (23.3)
HER2 enriched	60 (23.3)
Ki-67, n (%)	
<14%	160 (62.3)
≥14%	97 (37.7)
Chemotherapy regimen, n (%)	
AC	34 (13.2)
TC	61 (23.7)
TAC	135 (52.6)
Others	27 (10.5)

HER2, human epidermal growth factor receptor 2; AC, anthracycline and cyclophosphamide; TC, taxanes and cyclophosphamide; TAC, taxanes, anthracycline and cyclophosphamide.

Statistical analysis. The present study assessed the association between PLR and response to chemotherapy and pCR by

Table II. Relationship between changes of the platelet-to-lymphocyte ratio and chemotherapeutic efficacy.

Pre-chemotherapy	Post-chemotherapy	PR (n=155)	Non-PR (n=102)	$\chi 2$	P-value
Low (132)	Low (68)	51	17	6.88	0.009
	High (64)	34	30		
High (125)	Low (60)	41	19	7.12	0.008
	High (65)	29	36		

PR, partial response.

employing the χ^2 test. For both univariate and multivariate analysis, it employed the logistic regression model. All data were analyzed using IBM SPSS Statistics ver. 24.0 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient and tumor baseline characteristics. The present study included a total of 257 patients who underwent pre-treatment and post-treatment complete blood count, as shown in Table I. The average (median) age at diagnosis was 50 years, with a range of 34-70. At the time of diagnosis, T stage was cT3-4 in most instances (58.8%), and the prevailing histology was invasive ductal carcinoma (91.1%). In 37.7% of cases, there was a high expression of Ki-67 (≥14%) and 45.1% of tumors were classified as G1, indicating good differentiation. Of the patients, 23.3% had a HER2-positive subtype, 23.3% TN subtype, 44.1% Luminal subtype and 9.3% Luminal B subtype. Every patient underwent a minimum of six cycles of NACT. Following NACT, modified mastectomy was performed on 181 individuals (70.4%), whereas the remaining 76 patients (29.6%) opted for breast-conserving surgery.

Relationship between changes of PLR and chemotherapeutic efficacy. In order to establish the association between PLR variation and the effectiveness of chemotherapy, blood samples, magnetic resonance imaging and ultrasound assessments were conducted concurrently prior to the third cycle of NACT. In the present study, the cutoff value of high or low for pre-treatment or post-treatment PLR were the mean of the study population. After two cycles of chemotherapy, 68 (51.5%) patients in the PLR group with low pre-treatment levels maintained their low levels, while 64 (48.5%) patients transitioned to the high level group. In the meantime, among the high pre-treatment PLR group, 65 (52.0%) patients maintained a high level after two cycles of chemotherapy, while 60 (48.0%) patients shifted to the low level group (Table II). Patients who stayed in or moved to the low PLR category following two cycles of NACT demonstrated enhanced effectiveness of chemotherapy, in contrast to those who stayed in or moved to the high PLR category.

Association between PLR and pCR. A total of 75 patients (29.2%) obtained a pCR following NACT. In univariate analysis (Table III), classical indicators of poor prognosis in breast cancer, such as molecular subtype, tumor grade, and Ki-67, were found to be associated with pCR.

In univariate analysis, it was found that patients with a low PLR before treatment did not show a significant association with pCR. However, a significantly higher rate of pCR was observed in patients with a low PLR following treatment (P=0.075 and P=0.012, respectively). This finding suggested that post-treatment PLR may have a stronger effect on pCR compared with pre-treatment PLR. In univariate analysis (Table III), patients with ΔPLR<0 had higher rates of pCR compared with those with ΔPLR ≥0 (P=0.008) when combined.

In the analysis of multiple variables, excluding molecular subtypes and tumor grade, the significance of ΔPLR persisted (Table IV). Patients with ΔPLR<0 had a greater likelihood of achieving pCR compared with those with ΔPLR ≥0 (OR 2.07, 95% CI 1.13-3.80, P=0.018).

Discussion

Earlier studies have shown that markers of inflammation, like NLR and PLR, could potentially serve as predictive factors for pCR following NACT in breast cancer (10-12,16-18). Nevertheless, while these studies primarily examined the initial or pre-treatment condition of inflammatory markers, only a limited number of studies assessed the changes of inflammatory markers throughout or following the treatment. To the best of the authors' knowledge, the present study is the first to uncover that the early changes of PLR following two cycles of NACT are associated with neoadjuvant chemotherapy response and predict pCR in breast cancer.

For the current study, the analysis focused on three inflammatory markers and two different time points, namely pre-treatment PLR, post-treatment PLR, and ΔPLR before NACT and after two cycles of NACT, in order to assess chemotherapy response and pCR. In the multivariate analysis, only ΔPLR emerged as the sole independent predictive factor. The interpretation of this outcome suggests that ΔPLR was a more significant predictor for pCR compared with the absolute values of pre-treatment PLR or post-treatment PLR. Patients with ΔPLR <0 exhibited higher rates of pCR compared with those with ΔPLR ≥0, as demonstrated.

Until now, the underlying mechanism responsible for ΔPLR and chemotherapy response and pCR in breast cancer remained poorly understood. Some biological mechanisms could contribute to the relationship.

The inflammation status and immune response in the tumor microenvironment affect tumor development, progression and metastasis in individuals with cancer (19-21). In the

Table III. Association of patient/tumor characteristics to pCR in univariate analysis.

	Achieved pCR, n (%)		
Variable	Yes	No	P-value
Patients	75 (29.1)	182 (70.9)	
Age group			0.603
<50 years	34 (45.3)	89 (48.9)	
≥50 years	41 (54.7)	93 (51.1)	
Menopausal status			0.679
Pre-menopausal	28 (37.3)	73 (40.1)	
Post-menopausal	47 (62.7)	109 (59.9)	
Histologic type			0.074
Invasive ductal carcinoma	72 (96.0)	162 (89.0)	
Others	3 (4.0)	20 (11.0)	
T Stage			0.158
cT 1-2	36 (48.0)	70 (38.5)	
cT3-4	39 (52.0)	112 (61.5)	
Nodal status			0.531
Positive	43 (57.3)	112 (61.5)	
Negative	32 (42.7)	70 (38.5)	
Grade			**0.047**
G1	25 (33.3)	91 (50.0)	
G2	27 (36.0)	46 (25.3)	
G3	23 (30.7)	45 (24.7)	
Hormone receptor			**<0.001**
Positive	32 (42.7)	121 (66.5)	
Negative	43 (57.3)	61 (33.5)	
HER2			**<0.001**
Positive	33 (44.0)	27 (14.8)	
Negative	42 (56.0)	155 (85.2)	
Molecular subtype			**<0.001**
Luminal A	24 (32.0)	89 (48.9)	
Luminal B	2 (2.7)	22 (12.1)	
Triple Negative	16 (21.3)	44 (24.2)	
HER2 enriched	33 (44.0)	27 (14.8)	
Ki-67			**0.006**
<14%	37 (49.3)	123 (67.6)	
≥14%	38 (50.7)	59 (32.4)	
Chemotherapy regimen			0.078
AC	8 (10.7)	26 (14.3)	
TC	12 (16.0)	40 (22.0)	
TAC	54 (72.0)	103 (56.6)	
Others	1 (1.3)	13 (7.1)	
Surgery			0.584
Breast-conserving surgery	24 (32.0)	52 (28.6)	
Modified mastectomy	51 (68.0)	130 (71.4)	
ΔPLR			**0.008**
<0	47 (62.7)	81 (44.5)	
≥0	28 (37.3)	101 (55.5)	

Variable	Achieved pCR, n (mean)	P-value	Variable
Pre-treatment PLR			0.075
High	30 (40.0)	95 (52.2)	
Low	45 (60.0)	87 (47.8)	

Table III. Continued.

Variable	Achieved pCR, n (mean)	P-value	Variable
Post-treatment PLR			**0.012**
High	25 (33.3)	92 (50.5)	
Low	50 (66.7)	90 (49.5)	

Figures in bold represent significant P-values. pCR, pathologic complete response; HER2, human epidermal growth factor receptor 2; AC, anthracycline and cyclophosphamide; TC, taxanes and cyclophosphamide; TAC, taxanes, anthracycline and cyclophosphamide; PLR, platelet-to-lymphocyte ratio.

Table IV. Association of patient/tumor characteristics to pCR in multivariate analysis.

Variable	OR	95% CI	P-value
Grade (2/3 vs. 1)	2.34	1.25-4.37	**0.008**
TN/HER2+ vs. Luminal A/B	2.66	1.36-5.22	**0.004**
Ki-67 (>14% vs. ≤14%)	1.58	0.80-3.13	0.190
Post-treatment PLR (Low vs. High)	1.54	0.78-3.04	0.210
ΔPLR (<0 vs. ≥0)	2.07	1.13-3.80	**0.018**

pCR, pathologic complete response; OR, odds ratio; CI, confidence interval; PLR, platelet-to-lymphocyte ratio.

PLR, 'P' is regarded as a pro-tumor element, which has been demonstrated to release various cellular growth factors, such as transforming growth factor beta, platelet-derived growth factor, and vascular endothelial growth factor. These growth factors have the potential to promote tumor growth and the formation of new blood vessels angiogenesis (22-24). On the other hand, 'L' is regarded as an anti-cancer element that has a crucial function in monitoring the immune system against tumors. It can effectively inhibit tumor growth through its cytotoxic properties and ability to induce apoptosis (25,26). Increased lymphocyte infiltration has been correlated with higher pCR rate and an improved prognosis in breast cancer patients who received NACT (27,28). Therefore, when taken together, PLR could act as a marker that reflects the balance between host inflammatory response and immune response. When there is an elevated number of platelets and/or a decreased number of lymphocytes, an increased PLR can lead to an unfavorable outcome for various types of cancer (29,30).

Previous studies have mainly focused on baseline inflammatory status, before the treatment has started. The value of an inflammatory marker at this time may only reflect the status of the disease and not yet reflect the response to treatment. However, the changes of inflammatory marker during the treatment may reflect the response of the tumor to treatment and can improve the prediction of the subsequent outcome of the tumor. Therefore, ΔPLR was expected to be a more predictive factor compared with pre-treatment or post-treatment PLR. The changes of PLR indicate the fluctuation in the host's inflammatory and immune responses during treatment, offering potential for early assessment of treatment effectiveness. If the ΔPLR is <0 following the treatment, it indicates that the balance was tipped in favor of anti-tumor immune response. Otherwise, if ΔPLR is ≥0 following treatment, it indicated that the balance was tipped in favor of pro-tumor inflammatory response. The present study is consistent with this hypothesis.

Prior research has concentrated on various types of tumors, each exhibiting distinct levels of inflammation (31). These studies focus on different tumors, which tend to have different inflammatory status. Even in breast cancer alone, different age, ethnicity, stage and subtypes correspond with different immune response and therefore different inflammatory levels (30,32,33). Thus, there was no clinically recognized cut-off value for PLR. Unlike those, the present study focused on the changes in the level of blood inflammatory markers. It is not an absolute cut-off value, but a change variable, which is less affected by chemotherapy and other factors than pre-treatment or post-treatment PLR. In previous studies, certain researchers have demonstrated that changes in NLR or PLR following chemotherapy are associated with the response to chemotherapy or the prediction of prognosis in individuals diagnosed with gastric cancer (34), esophageal cancer (35), oesophago-gastric adenocarcinoma (36), and colon cancer (37). The present study revealed that the early changes of PLR serve a crucial role in predicting the response to NACT in breast cancer.

According to guidelines for neoadjuvant treatment of breast cancer, the clinical response needs to be evaluated every two cycles during the NACT treatment (38). Therefore, the present study chose the ΔPLR during the first two courses of NACT in order to early assess the NACT response. Moreover, ΔPLR in the following courses of NACT could also be monitored and analyzed to assess NACT response. However, if pCR can be predicted in an earlier course, it seems more helpful for clinician to predict the biological behavior of breast cancer accurately and make the treatment programs individualized

for the patients, such as changing chemotherapy regimens or deciding for surgery as early as possible.

Although the present study is a longitudinal study, which can minimize sample heterogeneity, it has certain restrictions. Due to the retrospective nature of this study, its limitations are dependent on the inherent quality of data recording and collection. Ideally, it would be preferable to evaluate inflammatory markers within the tumor together analyzing cells in the peripheral blood. However, those samples had not been obtained from these patients during NACT. Moreover, this study analyzed the PLR values before and after two cycles of NACT, but a further time point is needed to determine whether the prognosis varies along the chemotherapy period. For example, PLR values could be monitored every cycle to assess NACT response.

According to the data of the present study, ΔPLR may serve as more accurate predictor for chemotherapy response and pCR in breast cancer compared with the PLR values before or after treatment. With this marker, a clinician could predict early the biological behavior of breast cancer and make treatment programs individualized for the patients.

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Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Authors' contributions

YG and JD confirm the authenticity of all the raw data. YG, JD and JT conceived and designed the experiments; ZY and JT analyzed the data; JH contributed materials and analysis tools; JD and JT wrote the paper; JT and YG reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This research was a retrospective study without other diagnostic or therapeutic measures; therefore, informed consent was waived. The project was approved by the Ethics Committee of Chengdu Fifth People's Hospital on January 13, 2022 (reference K2021-053-01).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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