

Platelet To Lymphocyte Ratio Relationship With Neoadjuvant Chemotherapy Of Caf Regimen Response In Locally Advanced Breast Cancer Patients

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Abstract

Background: Chemotherapy in breast cancer can be given as neoadjuvant or adjuvant therapy. The response to neoadjuvant chemotherapy is very important in cancer management, especially in locally advanced breast cancer, therefore predictive factors which can predict chemotherapy response are very important. Platelet to lymphocyte ratio is a simple examination, which has been used as predictive factor in various cancer. This study will be focussing on locally advanced breast cancer.

Method: The study design is prospective cohort study. The research subjects examined the levels of platelets and lymphocytes in the blood before chemotherapy. Blood was drawn 1 day before the first chemotherapy session. Then the patient's clinical response was assessed after 3 cycles of chemotherapy. Each cycle is carried out at intervals of 3 weeks. Furthermore, the platelet to lymphocyte ratio and chemotherapy response will be assessed and analyzed.

Results: The research subjects consisted of 35 women. In this study, it was found that the mean value of platelets was $388,228 \pm 141.5$ g / dl, with a maximum value of 834,000 g / dl and a minimum of 206,000 g / dl. In the lymphocyte, the mean results were $2,025 \pm 759$ mg / l with a maximum lymphocyte value of 4,210 g / dl and a minimum of 800 g / dl. From the results of this study, the mean platelet / lymphocyte ratio was 232.9 ± 212.9 uL with a minimum value of 80.51 uL and a maximum of 1052 uL. In this study, it was found that most of the patients experienced a partial response in 23 patients (65.7%) and it was found that there was a significant relationship between the platelet / lymphocyte ratio and the clinical response of local advanced breast cancer patients with p value = 0.028 (p. <0.05)

Conclusion: There is significant relationship between the platelet / lymphocyte ratio and the clinical response of chemotherapy in locally advanced breast cancer patients. The higher the platelet to lymphocyte ratio, worse chemotherapy response is expected.

Keywords: locally advanced breast cancer; platelet to lymphocyte ratio, chemotherapy, neoadjuvant

Background

Chemotherapy in breast cancer can be given in neoadjuvant or adjuvant ways. The response to neoadjuvant chemotherapy is very important in cancer management, especially in locally advanced breast cancer, so predictive factors to predict chemotherapy response are very important to know. There are many

studies that discuss several predictive factors that are used, including: mitotic index and tumor differentiation and pleomorphism. Tumors can be differentiated good, moderate, and bad (grade 1, 2, or 3).¹ Grade 3 tumors have a 4.4 times higher relative risk of recurrence compared with grade 1. Lymphovascular invasion of several studies reported a risk of recurrence of 38% when present compared with 22% in cases where LVI

was absent. Histopathologic types, tubular, mucinous, tubulolobular, and cribriform breast tumors have the best prognosis. These tumors have an overall survival or Overall Survival (OS) of 10 years in 80% of cases. Ductal, lobular solid, and mixed-type (ductal and lobular) tumors have 10-year OS in only 50% of cases. The worst prognosis occurs with inflammatory carcinoma, which has a 10-year OS in 30% of cases. A study of breast cancer subtypes found that patients with positive hormone receptors had a higher percentage of 5-year DFS and OS. Her2 / neu expression can be used as a predictive factor for a patient's response to chemotherapy. Tumors with Her2 neu expression respond well and have a better survival rate than Her2 neu negative tumors, when treated with anthracycline-based chemotherapy. The rate of tumor proliferation can be measured by KI-67, mitotic index, and S-phase fraction, Neutrophil Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) ². Immunohistochemical examination (IHC) is needed in the treatment of breast cancer to determine the submolecular type of cancer. Based on these molecular subtypes, prognostic and predictive of breast cancer therapy can be determined. Based on CPI examination, there are four types of breast cancer, namely luminal types (luminal A and B), HER2-enriched types, and triple negative / basal like. Luminal types will respond to hormonal therapy, while other types will respond with chemotherapy if needed. However, currently in Indonesia there are only 17 hospitals that can carry out IHC examinations. Hospital Type B does not yet have CPI examination facilities, so to complete the examination it is necessary to carry out further examinations at the referral hospital. Due to limitations, there are some patients who discontinue IHC examinations and continue to receive anthracycline-based chemotherapy.

Currently there are several simple and easy to do biomarkers that can be predictors of neoadjuvant chemotherapy (NAC) response, one of which is the platelet lymphocyte ratio (PLR). PLR is one of the hematological parameters that can be used to determine the NAC response in patients with breast cancer. PLR can be used as an indicator to evaluate the systemic inflammatory response in cancer patients. Based on the results of research by Asano et al., 2016 (cut off point PLR 150), it was found that low PLR had a positive response to NAC in LABC patients. PLR is a marker that is easy, cheap and fast to calculate, but not many

people know its role. So it is hoped that by knowing the PLR value, clinical later can make the basis of education to LABC patients about prognosis and prediction of chemotherapy response. PLR in peripheral blood before surgery was reported to represent an independent predictive factor in breast cancer ³.

According to a study by Asano and colleagues, the platelet / lymphocyte or platelet to lymphocyte ratio (PLR) was reported as a predictive and prognostic biomarker in the breast cancer group of patients, high PLR increased the risk of negative clinical response threefold in the neoadjuvant setting. However, according to a 2018 Cuello-López study, PLR was not associated with the clinical picture of breast cancer patients receiving neoadjuvant therapy. From these controversial results, the authors are interested in conducting a study on the relationship between the platelet / lymphocyte ratio values at RSUD Dr. Soetomo Surabaya to assess the therapeutic response of local advanced breast cancer patients receiving neoadjuvant CAF chemotherapy.

Method

Research in the form of observational analytic research with *prospective cohort* design. Female patients with locally advanced breast cancer who met the study inclusion and exclusion criteria were given an explanation of the purpose and benefits of the examination, and were asked for consent to participate in the study by signing the informed consent and the informed consent. Furthermore, general data of the subjects such as name, age, gender, address and telephone number are recorded. Other data is recorded according to the data collection form. The research subjects examined the levels of platelets and lymphocytes in the blood before chemotherapy and every chemotherapy session. Blood was drawn 1 day before the chemotherapy session 1. Then the patient's clinical response was assessed after 3 cycles of chemotherapy. Each cycle is carried out at intervals of 3 weeks. Furthermore, the platelet / lymphocyte ratio will be assessed and its relationship with the clinical response of local advanced breast cancer patients receiving CAF neoadjuvant chemotherapy.

Results

The study subjects consisted of 35 women (100%), with the largest age being 35 - 50 years, namely 19

patients (54.3%) with a mean age of 47.94 ± 10.5 . In this study, it was found that the most subtype of breast cancer was luminal A as many as 11 patients (31.4%) followed by Luminal B-like (positive HER-2) as many as 7 patients (20%) with the most type of anatomical pathology was ductal carcinoma, namely 25 patients (71.4%). Characteristics of research subjects can be seen in Table 1.

Table 1. Characteristics of Research Subject

Subject's Characteristics		Response (+)	Response (-)	Total	Mean	P value
Age	< 35 years old	3 10.7%	0 0.0%	3 8.6%	47.94 ± 10.5	0.386
	35 - 50 years old	16 57.1%	3 42.9%	19 54.3%		
	> 50 years old	9 32.1%	4 57.1%	13 37.1%		
Histopathology	Ductal Carcinoma	18 64.3%	7 100.0%	25 71.4%		0.61
	Non-Ductal Carcinoma	10 35.7%	0 0.0%	10 28.6%		
Molecular Subtype	Luminal A	5 17.9%	6 85.7%	11 31.4%		0.013
	Luminal B-like (HER-2 positive)	7 25.0%	0 0.0%	7 20.0%		
	Luminal B-like (HER-2 negative)	6 21.4%	0 0.0%	6 17.1%		
	Basal like	5 17.9%	1 14.3%	6 17.1%		
	Erb-B2 overexpression	5 17.9%	0 0.0%	5 14.3%		

From the results of data analysis between the characteristics between the patient's age and the chemotherapy response, there was no significant difference (95% CI; p = 0.386). From the analysis of the breast cancer pathology group, there was no significant difference between groups in chemotherapy response (95% CI; p = 0.61). Meanwhile, from the analysis of the cancer pathology subtype group, there

was also a significant difference between groups with chemotherapy response (95% CI; p = 0.013). This can be a confounding factor in this study.

In this study, it was found that out of 35 patients, the mean value of platelets was $388,228 \pm 141.5$ g / dl, with a maximum value of 834,000 g / dl and a minimum of 206,000 g / dl. In the lymphocyte results, the mean

results were $2,025 \pm 759$ mg / l with a maximum lymphocyte value of 4,210 g / dl and a minimum of 800 g / dl. From the results of this study, the mean platelet / lymphocyte ratio was 232.9 ± 212.9 uL with a minimum value of 80.51 uL and a maximum of 1052 uL. The thrombocyte / lymphocyte ratio in research subjects is shown in Table 2.

Table 2. Platelet to Lymphocyte ratio in Research Subjects

	N	Minimum	Maximum	Mean	Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Statistic
Trombosit	35	206.000	834.000	388.228	141.583
Limfosit	35	800	4.210	2.025	759
Ratio	35	80.51	1052	232.9	212.9

Platelet to lymphocyte ratio value: The platelet to lymphocyte ratio value is the platelet type count divided by the lymphocyte type count. The results of the examination of platelets were compared to lymphocytes in the blood in uL units. The values will be divided into two categories, namely low with a value of <150 uL and high with a value of >150 uL. In this study, it was found that most of the LABC breast cancer patients had a low platelet / lymphocyte ratio, namely 18 patients (51.4%). PLR categories of research subjects are seen in Table 3.

Table 3. Platelet to Lymphocyte ratio categories in Research Subjects

Category	n	Percentage (%)
High	17	48.6
Low	18	51.4
Total	35	100.0

The clinical response to chemotherapy is an evaluation of the change in tumor size as measured objectively through physical examination, divided into four categories, namely: progressive disease, stable disease, partial response, and complete response. In this study, it was found that most of the patients experienced a partial response, as many as 23 patients (65.7%). The clinical response is shown in Table 4.

Table 4. Clinical response in Research Subjects

Response	n	Percentage (%)
Complete Response	5	14.3
Partial Response	23	65.7
Stable Disease	7	20.0
Progressive disease	0	0
Total	36	100.0

In this study, a relationship test of the independent and dependent variables in the form of ordinal and nominal data was carried out. From the research data obtained that the majority of patients who had a (+) response had a low platelet / lymphocyte ratio.

Table 5. Cross table of PLR and Chemotherapy response

		Chemotherapy Response		Total	p	RR
		Positive Response	Negative Response			
PLR Category	Low	17	1	18	0,028	9,2
		60.7%	14.3%	51.4%		
	High	11	6	17		
		39.3%	85.7%	48.6%		
Total		28	7	35		

The relationship between the thrombocyte / lymphocyte ratio and the clinical response of chemotherapy in locally advanced breast cancer patients was tested using a chi-square test, it was found that there was a significant relationship between the platelet / lymphocyte ratio and the clinical response of local advanced breast cancer patients with a p value = 0.028 ($p < 0.05$), which means that there is a significant relationship between the platelet / lymphocyte ratio and the clinical response to CAF chemotherapy. In this study, it was found that the relative risk was 9.2, meaning that someone who has a low platelet / lymphocyte ratio has a 9.2x higher chance of having a good chemotherapy response than those who have a high platelet / lymphocyte ratio as shown in Table 5.

Discussion

In this study, it was found that most of the LABC breast cancer patients had a low platelet / lymphocyte ratio (51.4%). and it was found that most of the patients experienced a partial response (65.7%). The relationship between the platelet / lymphocyte ratio showed that there was a significant relationship between the platelet / lymphocyte ratio and the clinical response of locally

advanced breast cancer patients with a p value = 0.028 ($p < 0.05$), which means that there was a significant relationship between the platelet / lymphocyte ratio. with the CAF chemotherapy response with a relative risk was 9.2. The results of this study are in line with previous studies in assessing the predictive value of platelet counts and the ratio to other immune cells - including lymphocytes and neutrophils - in the context of breast cancer. Breast cancer patients with a low platelet-to-lymphocyte ratio (PLR < 150) who were treated with neoadjuvant chemotherapy achieved a higher complete pathological response, regardless of tumor molecular subtype. Susceptibility to change under various conditions. Increased numbers of neutrophils and platelets are often caused by inflammatory diseases, such as connective tissue disorders, drug administration, bacterial disease, or viral infections. The most common cause of a low lymphocyte count is recent infection. In addition, lymphocytopenia can also be caused by infection, malnutrition, connective tissue disorders, heavy stress, intense physical exercise, and medical treatment⁴.

Research conducted by Kim et al. In 2019, in this study, HER-2-positive and TNBC tumors

showed the highest correlation between low PLR and rates of complete pathological response and prognosis. The study included a large number of HR-positive breast cancers in the survival analysis. PLR was significantly effective in determining the predictive value of breast cancer. However, in that study, a combination of NLR and PLR was suggested as a model for the CAF response with a potential role as a screening tool. Furthermore, the combination of NLR and PLR showed a significant predictive role in breast cancer patients receiving neoadjuvant chemotherapy⁵. For patients with breast cancer being treated with neoadjuvant chemotherapy, low PLR indicates high chemotherapy sensitivity, suggesting that PLR can function as a predictive marker of the therapeutic effect of neoadjuvant chemotherapy³.

Research by Asano et al. In the Japanese population, an association was found between low PLR ratio (cut-off: PLR <150), age (> 56 years) and postmenopausal status ($p = <0.001$). Krenn-Pilko in 2014, showed that a high PLR (cut-off: PLR > 292) was correlated with high lymph node involvement and high tumor rates ($p = <0.05$), while it was found that no correlation was found related to other clinicopathological variables. On the other hand, research by Koh et al. 2015 reported an association of height PLR (cut-off: PLR > 215) with age (> 50 years, $p = <0.01$) and tumor size (> 5 cm, $p = <0.01$), while no association were found with lymph node involvement or tumor grade ($p = 0.091$ and $p = 0.06$, respectively). In this study, PLR of patients receiving neoadjuvant therapy was not associated with clinical features including age ($p = 0.611$), menopausal status ($p = 0.209$), tumor rade ($p = 0.229$), tumor size ($p = 0.622$), lymph node involvement. clear ($p = 0.680$), and stage ($p = 0.570$)⁴. Tumor cells have been shown to induce the synthesis of platelet-stimulating factors that support growth, invasion and metastasis of primary tumors by several mechanisms. Thus, the blood platelet count device could be an indirect indicator of tumor activity. On the other hand, detection of high peripheral blood lymphocyte counts with antitumor activity - particularly CD8 + T cells would be an indicator of tumor suppression activity. Thus these data suggest that patients with low PLR will have higher antitumor activity, a better prognosis, and a better chemotherapy response. In a study by Asano and colleagues, PLR was reported as a predictive and predictive biomarker

in a group of breast cancer patients threefold negative in the neoadjuvant setting, since patients with low PLR showed higher levels of pCR, DFS, and OS. In a smaller cohort of breast cancer patients where a high PLR was independently associated with poor response to neoadjuvant chemotherapy. Results of the same studies^{6,7} showed that PLR was associated with pCR, being that patients with low PLR (<150) achieved higher pCR rates (35.1% vs 22.2%, $p = 0.03$). Overall, these data support the role of PLR as a predictive variable for pCR independent of tumor molecular subtypes. It is known that tumors with greater neoantigen synthesis - such as TN and Her2 - positive - can achieve a higher anti-tumor immune response by increasing the number of peripheral lymphocytes, and thereby potentiating the effect of neoadjuvant chemotherapy. This is supported by studies that suggest tumor infiltration lymphocyte (TIL) as a predictive biomarker of CPR in the neoadjuvant setting, especially in the early stages of Her2-positive and TN tumors. In addition, TIL is of predictive value, because high TIL counts are associated with improved overall survival, strongly supporting the idea that immune system activation is essential for survival outcomes. In this study, there were patients who had a platelet level of more than 800,000 based on data tracing, that the patient was currently in a respiratory tract infection condition. Based on the literature, patients with breast cancer are susceptible to infection due to decreased immune conditions. Based on the literature the causes of thrombocytosis include thrombocytosis is a clinical condition in which a platelet count exceeds 2 standard deviation (SD) above the average. Some literature mentions thrombocytosis with a number that varies between 400 - 1000 x 10³ / L. An excessive number of platelets can be caused by many factors, but can be grouped into three conditions, namely: increased production caused by stimulation (reactive thrombocytosis), primary disorders such as myeloproliferative or dysplasia syndrome (essential), thrombocytosis associated with hematological diseases such as chronic leukemia and polycythemia, reactive thrombocytosis is a secondary response to several conditions such as trauma, infection, inflammation, and immune disorders. Predisposing factors for reactive thrombocytosis are acute or chronic infections, hypoxemia, surgery, trauma, malignancy, bleeding, stress and splenectomy which generally occur due to the

release of cytokines in response to infection or trauma. Patients generally have no complaints as well as clinical symptoms are not always found and only present in 30% of patients are thrombohemorrhagic events. Besides that, you can also find complaints of headaches, dizziness, paresthesia and facial phenomena.

Conclusion

There was a significant relationship between an increase in the platelet / lymphocyte ratio with a decrease in the response to chemotherapy neoadjuvant CAF in Locally Advanced Breast Cancer patients, where the higher the platelet / lymphocyte ratio, the lower the response to chemotherapy neoadjuvant CAF

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Bibliography

1. Tryfonidis K, Senkus E, Cardoso MJ, Cardoso F. Management of locally advanced breast cancer—perspectives and future directions. *Nat Rev Clin Oncol* [Internet]. 2015;12(3):147–62. Available from: <https://doi.org/10.1038/nrclinonc.2015.13>
2. Glissmeyer M. Reviewing prognostic factors in breast cancer management. *JAAPA*. 2007;20(5):42–6.
3. Asano Y, Kashiwagi S, Onoda N, Noda S, Kawajiri H, Takashima T, et al. Platelet-Lymphocyte Ratio as a Useful Predictor of the Therapeutic Effect of Neoadjuvant Chemotherapy in Breast Cancer. *PLoS One*. 2016;11(7):e0153459.
4. Cuello-López J, Fidalgo-Zapata A, López-Agudelo L, Vásquez-Trespalacios E. Platelet-To-lymphocyte ratio as a predictive factor of complete pathologic response to neoadjuvant chemotherapy in breast cancer. *PLoS One*. 2018;13(11):1–12.
5. Kim HY, Kim TH, Yoon HK, Lee A. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in predicting neoadjuvant chemotherapy response in breast cancer. *J Breast Cancer*. 2019;22(3):425–38.
6. Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High Platelet-to-Lymphocyte Ratio Predicts Poor Prognosis and Clinicopathological Characteristics in Patients with Breast Cancer: A Meta-Analysis. *Biomed Res Int*. 2017;2017.
7. Zhu Y, Si W, Sun Q, Qin B, Zhao W, Yang J. Platelet-lymphocyte ratio acts as an indicator of poor prognosis in patients with breast cancer. *Oncotarget*. 2017;8(1):1023–30.