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Platelet count, platelet lymphocyte ratio, and Ki67 as a predictive factor of neoadjuvant chemotherapy response in locally advanced breast cancer

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ABSTRACT

Background: Locally advanced breast cancer (LABC) is a term that refers to advanced non metastatic stage breast cancer. Neoadjuvant chemotherapy is one of the therapies given to patients with LABC. Many factors can affect the chemotherapy response, platelets produce growth factors, and cytokines promote angiogenesis and tumor growth. Inflammatory biomarkers such as platelet lymphocyte ratio (PLR) may indicate tumor progressiveness. The Ki67 proliferation index is a marker of the aggressiveness or growth of tumor cells. This study aimed to determine the correlation of platelet count, platelet lymphocyte ratio and Ki67 proliferation index before chemotherapy with neoadjuvant chemotherapy response.

Method: This research used the cohort retrospective design method. A sample of 155 patients was selected using a simple random sampling technique. The inclusion criteria of this research are having complete data about pre-treatment platelet, lymphocyte platelet ratio, Ki67 and the neoadjuvant chemotherapy response result assessed by the oncologist that is written in the medical record. Patient data from other types of cancer, chronic, systemic or autoimmune diseases are excluded from this research. The data of each variable was analyzed with the Spearman correlation test.

Result: There was no correlation between platelet count and neoadjuvant chemotherapy response (p=0.301). There was a negative correlation between the platelet lymphocyte ratio (p=0.026) and the Ki67 index (p=0.040) with neoadjuvant chemotherapy response.

Conclusion: Based on this study, it can be concluded that platelet count is not significant in relation to chemotherapy responses. The higher the platelet lymphocyte ratio and the proliferation index of Ki67, the lower the response to neoadjuvant chemotherapy.

Keywords: Chemotherapy Response, Ki67, Platelet Lymphocyte Ratio.
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INTRODUCTION

Breast cancer is the most common malignancy and the leading cause of death in women worldwide. Global Burden Cancer data in 2020, the number of new breast cancer cases reached 68,858 cases (16.6%) from a total of 396,914 new cancer cases in Indonesia. Meanwhile, the number of deaths reached more than 22 thousand cases.[1] Based on data from the Electronic Data Center at the Regional General Hospital Ulin Banjarmasin, there were 1,420 patients with breast cancer underwent hospitalization during 2017-2022.[2] Locally advanced breast cancer (LABC) is a term that refers to advanced non metastatic stage breast cancer there was a progression of disease in the breast and/or regional lymph nodes without any evidence of distant metastasis. The LABC group can be divided into (1) operable, T3N1 (2) Inoperable conditions, T4 and/or N2 to N3 clinical conditions, and Inflammatory Breast Cancer, T4d clinical conditions N0 to N3.[3]

Recently, many therapeutic modalities have been used with good outcomes, especially if the treatment was given in the early stages of the disease. However, when the cancer has no optimal treatment, the cancer will metastasize to the lungs, liver, bones or brain and cause various complications, also triggering a worsening of the condition and mortality. For LABC, the therapeutic modalities are neoadjuvant chemotherapy, surgery, radiotherapy, targeting therapy and hormonal therapy. Neoadjuvant chemotherapy is one of the therapies given to patients with LABC; it aims to reduce the tumor size from "inoperable" to "operable" so that surgical procedures can be performed. The response to neoadjuvant chemotherapy is influenced by many factors, including platelets, platelet lymphocyte ratio and the proliferation index of Ki67.[3]

Platelets secrete various growth factors and cytokines that promote angiogenesis, tumor growth, cancer cell invasion and metastasis either directly or indirectly. In women with breast cancer, platelet

increase correlates with poor prognosis. The ability of breast tumor cells to induce platelet aggregation correlates with their tumorigenesis and metastatic potential.[4] Inflammatory biomarkers such as platelet lymphocyte ratio (PLR) have been proposed as one of the progressive prognostic factors and chemosensitivity in various types of cancer. According to research conducted by Cuello-López J et al. against patients with breast cancer, tumor size, and histology grade, PLR is unrelated to age, menopausal lymph node involvement status, disease stage, estrogen receptor status and Ki67 proliferation index. However, in the group with a low lymphocyte platelet ratio, there was an increase in histopathological complete chemotherapy response.[5] The Ki67 proliferation index is used as a marker of aggressiveness or growth of tumor cells. Elevated levels of the Ki67 proliferation index are independent predictors of the response to neoadjuvant chemotherapy; according to Vörös A et al., high Ki67 proliferation index values are associated with complete pathological regression in breast cancer cells.[6]

Based on those mentioned above, this study aims to evaluate the correlation of platelet count, platelet lymphocyte ratio and Ki67 proliferation index before chemotherapy with neoadjuvant chemotherapy response.

METHODS

This cohort retrospective design study aims to analyze the correlation of pre-treatment platelet count, lymphocyte platelet ratio, and Ki67 with neoadjuvant chemotherapy response in locally advanced breast cancer patients at Ulin Banjarmasin Hospital. The population in this study were patients diagnosed with locally advanced breast cancer. The affordable population in this study was patients diagnosed with locally advanced breast cancer who carried out therapy in the oncology surgery department at Ulin Banjarmasin Hospital in 2021, with as many as 252 patients. This population was then calculated based on Slovin's formula, and a total sample of 155 patients data was obtained to select by simple random sampling technique.

The platelet and lymphocyte platelet ratio data was obtained from the pre-treatment laboratory result. The Ki67 proliferation index was obtained from the immunohistochemistry anatomic pathology result in the medical record. The inclusion criteria of this research are having complete data about pre-treatment platelet, lymphocyte platelet ratio, Ki67 and the neoadjuvant chemotherapy response result assisted by an oncologist that is written in the medical record. Patient data from other types of cancer, chronic, systemic or autoimmune diseases are excluded from this research.

The study results are presented as a table and a written description. Univariate analysis was carried out to see an overview of the frequency distribution of each variable studied, both bound variables in the form of chemotherapy responses and free variables, namely platelet count, PLR, and Ki67 proliferation index, statistically using the SPSS program. The Spearman correlation analysis test was carried out to analyze the correlation of free variables with bound variables.

RESULTS

The respondent characteristic of this study is described in Table 1, which shows the age distribution of most samples in the age group ≥ 45 years (75.0%), where this age is a high-risk age for breast cancer. The distribution of sample data is mostly luminal type B (39.0%) (Table 1).

The sample characteristic of the data is described in Table 2, where it was found that platelet variables had a minimum value of $77x10^3$/µL and a maximum value of 887 thousand/µL with an average value of $369.04x10^3$/µL. The minimum score in this study is included in the category of thrombocytopenia because the value is less than $150x10^3$/µL (Table 2). The maximum value in the number of platelet counts in this study was $887x10^3$/µL, which is included in the category of thrombocytosis; this can appear in conditions of increased levels of hydrogen peroxide in the blood due to oxidation stress due to systemic hypermetabolism, this can further trigger conditions of coagulation disorders such as thrombosis, vascular disorders, or an increased risk of metastatic in cancer. In this study, the average result of platelet values was found at $369.04x10^3$/µL, which is a normal value because it is in the range of 150 - $450x10^3$/µL (Table 2). The variable platelet-lymphocyte ratio has a minimum value of 77.8 and a maximum value of 840, with an average value of

Table 1. Respondent characteristics

Variable	n	%
Age		
Risk (≥ 45 years old)	116	75.0
No Risk (< 45 years old)	39	25.0
Subtype		
Luminal A	19	12.0
Luminal B	61	39.0
Her-2 Subtype	34	22.0
Triple Negative	41	27.0

Table 2. Descriptive data of variable

No.	Variable	Minimal	Maximal	Mean	Average
1.	Platelet	$77x10^3$/µL	$887x10^3$/µL	$375x10^3$/µL	$369.04x10^3$/µL
2.	Lymphocyte	$0.25x10^3$/µL	$4.20x10^3$/µL	$1.2x10^3$/µL	$1.21x10^3$/µL
3.	PLR	77.8	840	305	318.60

Table 3. Data analysis of correlation

Variable	Coefficient Correlation	p-value
Platelet – Recist	-0.084	0.301
PLR – Recist	-0.179	0.026*
KI67 – Recist	-0.166	0.040*

Non-parametric correlation test; *Statistically significant if p-value less than 0.05.

318.60 (Table 2). For the Ki67 variable, most groups were obtained in Ki67 with a value of >20%, as many as 101 (65%). This shows the proliferation rate of tumor cells in this study shows that newly diagnosed tumors have not received a therapeutic intervention. The variable response to RECIST chemotherapy was obtained in most groups in Partial Responses of as many as 125 patients (80%).

As seen in Table 3, there's no correlation between platelet count and neoadjuvant chemotherapy response (p-value: 0.301). There was a negative correlation between the platelet lymphocyte ratio (p-value: 0.026) and the Ki67 index (p-value: 0.040) with neoadjuvant chemotherapy response (Table 3).

DISCUSSION

The decline in the immune system that begins at this age has an important role in the high risk of breast cancer. Laamiri FZ et al. mentioned that the age group of ≥ 45 years is more at risk for breast cancer due to several factors, including late menopause, oral contraceptives and family history at the first level, which is a condition of high estrogen exposure.[7] Another study that stated the distribution of patients with breast cancer was mostly over the years old was put forward by Elmika E et al., who examined the epidemiology of cases at one of the hospitals in Makassar. In 2019 there were 70.8% of new breast cancer cases in the age group of ≥ 45 years.[8]

The distribution of sample data is mostly luminal type B, according to previous research by Widiana IK et al., which examined data from 1260 breast cancer cases in Indonesia and obtained the most breast cancer case data dominated by cancer with positive hormone receptors (luminal B 43.2%, luminal A 21.7%).[9] This is in accordance with the etiology of the distribution of breast cancer patients aged ≥ 45 years caused by late menopause, oral contraceptives and family history at the first level, which is related to the accumulation of estrogen and progesterone hormone levels in the body.[7]

The thrombocytopenia condition in this study can occur at a young age (< 18 years) and too old age (>60 years); it can be caused by the presence of changes in hematopoietic stem cells as a result of systemic metabolism.[10] This is in line with research by Faria AVS et al., which states that the age range between 40-59 years is the age at which platelet levels are in stable condition. Even in cancer conditions, the incidence of changes in platelet values in this age range is not always meaningful except in metastatic conditions.[10]

The average PLR value increase can be caused by several conditions, including in breast cancer with a triple negative type, in the condition of body immunity decreases due to local immunosuppression by tumors, characterized by the suppression of immune factors such as NK cells by platelets followed by a decrease in lymphocyte rating.[11]

For the Ki67 variable, most groups were obtained in Ki67 with a value of >20%. This shows the proliferation rate of tumor cells in this study shows that newly diagnosed tumors have not received a therapeutic intervention. This is in line with a study conducted by Moazed V et al., which examined 55 breast cancer patients there where 54.5% of patients had high ki67 expression, and it decreased significantly after receiving chemotherapy.[12]

The variable response to RECIST chemotherapy was obtained in most groups in Partial Responses. This shows the effectiveness of the therapy carried out by breast cancer patients at Ulin Hospital. In this study, the modality of the chemotherapy regimen studied was in patients undergoing neoadjuvant chemotherapy using anthracycline-based regimens, namely 5-Fluorouracil, doxorubicin, and cyclophosphamide (FAC). This type of regimen was chosen because it is a chemotherapy neoadjuvant regimen for Locally advanced breast cancer that is commonly used in Indonesia because it has work effectiveness that is no different from other regimens but has better cost efficiency than other neoadjuvant regimens.[13]

This study found a negative correlation between platelet count and RECIST criteria chemotherapy response, although the correlation was weak and not statistically meaningful. The negative correlation between the two variables suggests that the higher the platelet count, the lower the category of RECIST criteria. This is because platelet granules contain various growth factors secreted immediately after platelet activation; this is where platelet mechanisms are involved in tumor and metastatic development. Tumor cells cannot survive without avoiding natural killer (NK) cell attacks. Platelets envelop tumor cells in a thrombus to escape the detection of NK cells, allowing them to circulate through the bloodstream. Platelets can also secrete TGF-β, a multifunctional cytokine that modulates cell proliferation, growth, differentiation, adhesion and survival. In addition, platelets also play a role in the production of extracellular matrix proteins that can increase the metastatic potential and reduce the cytotoxicity of NK cells and the production of IFN-γ. Platelets can also store and release growth factors such as the Vascular Endothelial Growth Factor (VEGF) and Platelet-derived growth factor (PDGF), essential for tumor growth and vascular stability when stimulated by external sources. In addition, platelets can prevent chemotherapy-induced apoptosis in cancer cells.[14]

The correlation between platelet count and the meaningless RECIST neoadjuvant chemotherapy response can be caused by other factors in platelets that may affect the outcome, including platelet volume. As mentioned by Tera Y et al. in their research which states that there is no relationship between the number of platelets count, the size of the tumor and its grading, and another factor that affects the number of platelets is the volume of platelets themselves, as mentioned by Mutlu H et al. in their research, there is a negative correlation between the mean platelet volume (MPV), where the MPV with a low value (<8.15) indicates a better chemotherapy response direction.[15,16] Therefore, platelet activation differs not only from the number of counts but also from the large volume of platelets themselves.

This study showed a negative correlation between the platelet lymphocyte ratio and the chemotherapy response of the RECIST criteria. It shows that the higher the platelet lymphocyte ratio, the lower the category of RECIST criteria; otherwise, the lower the platelet lymphocyte ratio, the better the prognosis of the RECIST chemotherapy response. Tumor cells have been shown to

induce the synthesis of platelet stimulating factor, which supports the growth, invasion and metastasis of primary tumors through several mechanisms.[17] The calculation of peripheral blood platelet count can indirectly indicate high or low tumor activity; on the other hand, detecting a high number of peripheral lymphocytes in the presence of antitumor activity will be an indicator of tumor suppression activity. Because lymphocytes can inhibit the proliferation of tumor cells and their metastatic activity through their infiltration of cancer cells. Platelets play a role in tumor development in the metastatic cascade, protecting tumor cells from immune surveillance, regulating tumor cell invasion, and angiogenesis.[17,18]

The release of platelet-derived factors stored in its granules causes platelets' inflammatory, proliferation, and proangiogenic activity to promote tumor growth, tissue invasion, and metastasis. Platelets also secrete thrombospondin-1, which facilitates the adhesion of tumor cells to the endothelium, encouraging extravasation in the metastatic cascade. Thrombospondin levels have been found to increase in women with gynecological malignancies. Once the tumor cells are out of circulation, the factors derived from the activated platelets can induce neoangiogenesis[18]. Lymphocytes are one part of white blood cells that play a role in the immune system. The count of lymphocytes serves as an indicator of immune system function. Their number is associated with the prognosis of solid tumors through their role in anti-neoplastic effects. It protects the host against tumor development through an apoptosis-inducing T-cell immune response. The normal range of lymphocyte count is 1,250- 4,000/UL.[19]

The platelet lymphocyte ratio (PLR) is the ratio calculation of the absolute count of platelets to the absolute count number of lymphocytes. A high PLR reflects a decrease in platelet count or an increase in lymphocyte count.[7] As Cuello-López J et al. mentioned in their study, a low PLR would indicate high antitumor activity, a better prognosis, and a better chemotherapy response.[5] This study found that the higher the PLR value, the lower the RECIST criteria, which means the worse the chemotherapy response obtained.

The results of this study on the correlation of ki67 with the response of RECIST chemotherapy do not correspond to the theory that cytotoxic therapy in chemotherapy works on the process of cell proliferation. So, tumors with a higher initial proliferation index benefit better if given chemotherapy than patients with a low initial proliferation index. However, in other studies, it is stated that there is a concept where a high proliferation rate will cause central hypoxia of the tumor, which will subsequently cause a poor chemotherapy response.[20]

Normal breast tissue oxygen levels average at pO2 65 mmHg, while in breast cancer, it is about 28 mmHg. Areas with low oxygen levels are commonly referred to as hypoxic regions. In tumors in a state of rapid proliferation and high metabolism, oxygen consumption is much greater than supply, resulting in a continuous decrease in oxygen content in the tumor microenvironment, giving rise to central hypoxia of the tumor. This further triggers cells to secrete vascular endothelial growth factor (VEGF) and other pro-vascular factors to accelerate tumor regeneration.[21] Another research that supports this theory is as proposed by Zhang Y et al., who state that central tumor hypoxia is caused by the rapid proliferation of tumor cells characterized by an increase in immunohistochemistry Ki67.[22] This will then trigger a condition of tumor resistance to therapy, resulting from DNA damage to tumor cells that are hypoxic and reduced perfusion around the tumor which will inhibit the distribution of chemotherapy regimens given to cells target.[21,22] Chemoresistance in central tumors experiencing hypoxia has also been cited in a study by Milani M et al. which examined 176 women with Locally advanced breast cancer who received chemotherapy with epirubicin regimens. The results showed that central tumor hypoxia characterized by increased levels of Hypoxia Inducible Factor (HIF) was negatively correlated with an increase in chemotherapy response. The higher the HIF level, the lower the chemotherapy response.[23-27]

This study found that the higher the proliferation index of Ki67, the lower the chemotherapy response. The limitation of this study was there was no specific data about platelet volume and central tumor hypoxia level corresponding to tumor cell progression in influencing neoadjuvant chemotherapy response. Future research can be suggested on the effects of central tumor hypoxia with its relation to tumor cell progression, morphology, and platelet volume in influencing response to neoadjuvant chemotherapy.

CONCLUSION

There is no correlation between platelet count and neoadjuvant chemotherapy response in Locally advanced breast cancer patients at Ulin Banjarmasin Hospital. There is a correlation between the platelet lymphocyte ratio and neoadjuvant chemotherapy response in Locally advanced breast cancer patients at Ulin Banjarmasin Hospital. There is a correlation between Ki67 and neoadjuvant chemotherapy response in Locally advanced breast cancer patients at Ulin Banjarmasin Hospital.

CONFLICT OF INTEREST

No known competing financial interests or personal relationships could have influenced the work report in this paper.

ETHICAL CLEARANCE

The Health Research Ethics Commission, Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia, declared this study ethically feasible. (No. 014/KEPK-FK ULM/EC/I/2023).

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AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, methodology, validation, formal analysis, review and editing until reporting the study results through publication.

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