INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

2024 July; 30 (3): 255 - 258
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Correlation between PLR and NLR with Tumor Size in Breast Cancer Patients

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ABSTRACT

Breast cancer is the most common malignancy in females globally and one of the main causes of cancer death. There are several markers of cancer-related inflammation to help predict the relationship between pathologic characteristics of breast cancer.The research objective was to analyze the correlation between PLR and NLR with associated tumor size in breast cancer. This was a retrospective study with a cross-sectional design. This study used secondary data from the medical records of breast cancer patients who met the inclusion criteria at Siti Khodijah Hospital, Sidoarjo from January 2021 to March 2023. The sample size was 54 subjects, patients with breast cancer confirmed by pathology anatomy. The exclusion criteria were patients with infection, autoimmune disease, and hematology disorder. All the subjects were female. The mean age at the time of breast cancer diagnosis was 50.18±10.23 years, range of 27-80 years old. Most of the patients were over 50 years as much as 28 (51.85 %), while there were 26 (48.14%) ≥ 50 years. The PLR range was 15.45-600.0, the NLR range was 0.58-9.98, tumor size range was 0.5-10.0 cm. Correlation between PLR and NLR with tumor size in breast cancer (p=0.351 and p=0.339). Correlation analysis showed that PLR and NLR had no significant correlation with tumor size(r=-0.129, p=0.351 and r=-0.133, p=0.339). In conclusion, there is no significant correlation between PLR and NLR with histopathology of tumor size inpatients with breast cancer.

Keywords: Breast cancer, PLR, NLR, tumor size

INTRODUCTION

Breast cancer is the most common malignancy in females globally, currently the highest-ranking cancer in terms of morbidity and mortality among females.[1,2] Breast cancer's metastatic spread is the main factor in breast cancer-related death. Data from the Global Cancer Observatory (GLOBOCAN) in 2020 shows that the incidence rate was 42,21 per 100,000, with an average death rate of 17 per 100,000. Total cases of breast cancer in Indonesia based on data from the Ministry of Health 2022, new cases reaching 68,858 cases (16.6%) out of a total of 396,914 cases in Indonesia, followed by a 9.6% rate of deaths caused by breast cancer.[3] Therefore, new biomarkers are urgently needed for early diagnosis and detection of breast cancer to benefit more breast cancer patients.

Risk factors closely related to an increased incidence of breast cancer include females, age over 50 years, hormonal factors, heredity, and lifestyle.[4] The breasts are anterior and partially lateral to the thorax.[5] The breast is drained by the lateral thoracic arteries, internal thoracic arteries, and thoracoacromial arteries.[5,6] Histopathological examination is the gold standard examination for breast cancer.[7] The stage of breast cancer needs to be determined before starting treatment. Generally, staging is determined based on the TNM classification of The American Joint Committee on Cancer (AJCC).[8,9]

The importance of systemic inflammatory responses in the development of cancer has long been recognized.[1] Inflammatory cells and their mediators in the tumor microenvironment are crucial for the growth and spread of malignancy in cancer patients. Numerous studies have shown that angiogenesis, immunosuppression, growth, and spread of cancer cells are all influenced by chronic inflammation. It has been established that Cancer Related Inflammation (CRI) is associated with a poor prognosis. Cancer cells can develop biologically malignant behaviors like metastasis, angiogenesis, invasion, and proliferation with the aid of CRI. Some combination indices, such as PLR and NLR, have been developed and proposed as straight forward criteria to evaluate systemic inflammation based on the quantity of circulating inflammatory cells. Better treatment and early detectionare needed.[10]

Numerous studies have revealed a relationship between the tumor and the tumor microenvironment, including inflammation and the immune response, affecting tumor progression and

prognosis.[11] Breast cancer occurs due to the loss of control and physiological mechanisms of cells causing abnormal, fast, and uncontrolled growth.[12] The body's inflammatory state and immune response to the tumor microenvironment have an impact on how a tumor develops, advances, and metastasizes.[2] Therefore, evaluating patients using simple, inexpensive, and easy detection can predict breast cancer outcomes.[13]

METHODS

This study was a retrospective study with a cross-sectional method. This study used secondary data from the medical records of Siti Khodijah Muhammadiyah Hospital patients from January 2021 until March 2023. The population of this study was Breast cancer patients in Siti Khodijah Muhammadiyah Hospital. The inclusion criteria were: patients diagnosed with breast cancer based on confirmed pathology reports, breast cancer patients with age above 18 years old, breast cancer patients with a laboratory test result of Complete Blood Count (CBC), and histopathology of tumor size. CBC was performed at baseline before treatment and surgery. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count, and the NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[14] The exclusion criteria were patients having other cancers either concurrently or previously diagnosed, patients with systemic autoimmune disease, hematology disorder, and patients with incomplete data.

This study has been ethically approved with article number 007/KET-KEPK/4-2023, on 20 April 2023, by the Ethics Committee for Health Research Siti Khodijah Muhammadiyah Hospital, Sidoarjo, Indonesia. The relationships between Platelet Lymphocite Ratio (PLR) and Neutrophil Lymphocite Ratio (NLR) with histopathology tumor size were assessed using the Spearman rank test. Statistical significance was defined as a p-value <0.05. Statistical Analysis was performed using the SPSS statistic software 19.

RESULTS AND DISCUSSIONS

This study included 54 breast cancer patients with complete blood counts prior to treatment or surgery. The basic characteristics of patients are shown in Table 1. The average age of breast cancer diagnosis was50.18±10.23 years (range 27-80) years old. The subjects were all female (100%), and most subjects were ≥ 50 years as much as 28 (51.85%) while there were 26 (48.14%) below 50 years old. The research by Takeuci *et al.* found that 21% of subjects were <50 years of age and 79% were ≥ 50 years. Age is an essential factor in the emergence of breast cancer. Epidemiological study shows that females over 50 years old are more likely to develop breast cancer than younger females.[4] Hormonal factors such as menstrual history (early menarche, late menopause) are at higher risk. Likewise, many hormones are associated with an increased incidence of breast cancer. The use of estrogen for more than 8-10 years has been proven effective in increasing the risk of developing breast cancer. First pregnancy at more than 35 years has a risk of 1.5-4 times greater than those aged 20-34 years, while nulliparity is 1.3-4 times the risk of developing breast cancer.[4]

Table 1. Characteristics of breast cancer patients

Criteria	Patients	n (%)
Gender	Female	54 (100%)
	Male	0 (0%)
Age (years)	Mean (50.18±10.23)	
	< 50 y.o	26 (48.14%)
	≥ 50 y.o	28 (51.85%)
	Range (27-80) years	
Grade	I	36 (66.7%)
	II	17 (31.5%)
	III	1 (1.9%)
Metastases	Yes	27 (50%)
	No	27 (50%)

Table 2 shows the distribution of hemoglobin, leukocytes, neutrophils, lymphocytes, and platelets in breast cancer patients. The Hb concentration in this study averaged 11.74±1.68 g/dL. The mean leukocyte count was 7.96±2.45x10^3/µL, the mean neutrophil count was 4.93±2.23 x 10^3/µL, the mean lymphocyte count was 2.09±0.91x10^3/µL, and the mean platelet count was 334.94±91.40x10^3/µL. The mean tumor size was 2.91±2.07 cm. In previous research by Cho, the average leukocytes, lymphocytes, and platelets, respectively, were 6.6±2.2x10^9/L, 2.1±0.8x10^9/L, and 259.1±61.6x10^9/L. The number of leukocytes, platelets, and lymphocytes found in this study wasalmost the same as Cho *et al.*[10]

Table 2. Laboratory values in breast cancer

Criteria	Mean±SD
Hemoglobin (g/dL)	11.74±1.68
Leukocyte (10^3/µL)	7.96±2.45
Neutrophil (10^3/µL)	4.93±2.31
Lymphocyte (10^3/µL)	2.09±0.91
Platelet (10^3/µL)	334,94±91.40
Tumor size (cm)	2.91±2.07

It has been accepted that patient-related factors, particularly the host response to systemic inflammation, have a significant impact on the prognosis of the disease in cancer patients. The pretreatment index or systemic inflammation score has been found by researchers to be able to predict survival in patients with a variety of cancer types. White blood cell counts, which include neutrophils, lymphocytes, and monocytes, as well as their combinations, such as NLR and PLR, have been highlighted in particular, since hematological tests are frequently carried out on cancer patients in clinical practice and biological research.[10] Lymphocytes, macrophages, neutrophils, and platelets play an important role in carcinogenesis, and the tumor systemically controls the immune system.[15] Thus, the production of inflammation may result in a rise in mutagenesis, predisposing to the accumulation of mutations in normal tissues.[16]

Table 3. Laboratory index value in breast cancer

Parameter	Median (Min-Max)	Mean±SD
PLR	(15.45-600.0)	194.6±113.2
NLR	(0.58-9.98)	2.88±2.22

The cytolytic activity of lymphocytes, natural killer cells, and activated Tcells is inhibited by neutrophils. Additionally, tumor-associated neutrophils encourage the remodeling of the extracellular matrix, which leads to the production of basic fibroblast growth factors, the migration of endothelial cells, and the separation of tumor cells from their main bulk. These occurrences ultimately lead to increased angiogenesis, tumor growth, and the development of the metastatic phenotype.[1]

The role of platelets in inflammation, malignant tumors, and hemostasis has been demonstrated by newly discovered evidence. Following the stimulation of megakaryocytes by inflammatory mediators generated by the tumor or its surroundings, such as IL-1, IL-3, and IL-6; platelets may accumulate. Such platelets can express high quantities of platelet-derived growth factor, vascular endothelial growth factor, and platelet factor 4, promoting the growth and spread of the tumor by encouraging tumor cell proliferation and adherence to other cells.[1] It has been discovered that these growth factors encourage tumor progression.[16] Numerous scoring systems based on inflammatory response molecules have been tested as prognostic indicators in various malignant cancers because tumor progression involves its interaction with inflammatory response molecules in its microenvironment.[1]

Lymphocytes play a crucial part in the immune surveillance of cancer, which aims to prevent the growth and metastasis of tumor cells. Through their cytotoxic action and induction of apoptosis in tumor cells, CD8 T cells and CD4 T cells can regulate the growth of tumors. Thus, the index of NLR and PLR serve as a new marker of malignant potential and prognosis in a variety of cancers.[1]

In this study at Table 3, the mean PLR was 194.69 (range 15.45–600.0), and the mean NLR was 2.91 (range 0.58–9.98). PLR, NLR, and tumor size data were all not normally distributed (p=0.000), so the correlation between the three variables was analyzed using Spearman's rank correlation.[17]

Table 4 shows there was no statistically significant difference, according to Spearman's rank correlation test results (p=0.351) between PLR and tumor size; likewise, for NLR, there was no significant relationship with tumor size (p=0.339) in breast cancer patients. Graziano showed that PLR had a significant correlation with tumor size p=0.025 and NLR had no significant correlation with p=0.118.[18] Cho reported that the average PLR and NLR were 142.41±192.78 and 1.89±1.38. Cho *et al*. found that PLR and NLR had no significant relationship with tumor size (p=0.464 and p=0.257, respectively). This study is in accordance with Yang, who found that PLR had no significant relationship with tumor size (p=0.857), and NLR has no significant correlation (p=0.311).[19] Takeuchi showed that PLR had no significant correlation with tumor size p=0.25 and NLR had a significant correlation (p=0.04). Anwar showed PLR results with tumor size p=0.03 and NLR with p=0.019, therefore NLR and PLR are potentially valuable as a reliable auxiliary prognostic marker in breast cancer.[20]

Table 4. Correlation between PLR, NLR with tumor size

Parameter	Tumor Size P	r_s
PLR	0.351	-0.129
NLR	0.339	-0.133

Based on Table 4, it was found that there was no significant correlation between PLR and tumor size, with a p-value of 0.351 (< 0.05) with a correlation strength of – 0.129 (weak). There was no significant correlation between NLR and tumor size, with a p-value of 0.339 and a correlation strength of – 0.133 (weak).

This study has several limitations. First, the study's retrospective design made it vulnerable to biases in

selection and analysis. Second, this study used secondary data, taking the patient's initial diagnosis based on clinical diagnosis, so researchers do not know the factors influencing PLR and NLR. Further research includingan examination of factors influencing PLR NLR is needed.

CONCLUSIONS AND SUGGESTIONS

According to this study, there is no relationship between PLR and NLR with histopathology and tumor size in breast cancer patients. To avoid bias, further research with supporting tests that support the exclusion criteria is needed.

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