

Platelet count and breast cancer stage

by Prihantono Prihantono

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Andi Fahdrin^a, Elridho Sampepajung^{b,*}, John Pieter^b, Firdaus Kasim^c, Nilam Smaradhan^b, Prihantono Prihantono^b, Nita Mariana^d, Daniel Sampepajung^b and Muhammad Faruk^a

^aDepartment of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

^bDivision of Oncology, Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

^cDepartment of Biostatistics, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia

^dDivision of Pediatric Surgery, Department of Surgery, Hasanuddin University, Makassar, Indonesia

Abstract

INTRODUCTION: The relationship between increased platelet count and cancer classification stage has long been established. The prevalence of thrombocytosis varies from 10% to 57% in cancer patients. The pathogenesis of thrombocytosis in malignancy is uncertain. However, there is evidence that tumor cells secrete humoral factors that can cause thrombocytosis. Preoperative thrombocytosis is a poor prognostic variable in malignancies. This study investigated the correlation between platelet count and breast cancer stage.

METHODS: This cross-sectional study was conducted from February 2020 to January 2021. Patient data were collected from medical records. The study population comprised breast cancer patients at Dr. Wahidin Sudirohusodo Makassar. The staging examinations were based on the tumor, node, metastasis (TNM) classification according to the American Joint Committee on Cancer (AJCC) 8th Edition.

RESULTS: The study group comprised 171 breast cancer patients of varying ages. Metastasis was present in five (2.92%) patients and absent in 166 (97.8%) patients. Analyses found no statistically significant differences between the three staging groups based on the platelet count ($p = 0.952$).

CONCLUSION: There was no statistically significant relationship between increased platelet count and staging according to the TNM classification in breast cancer patients.

Keywords: American Joint Committee on Cancer, breast cancer, platelet counts, staging

1. Introduction

Breast cancer is the most common malignancy and the leading cause of death in women worldwide [1,2]. It is the most common type of cancer in Indonesia, with an annual incidence of 18.6 cases per 100,000 individuals, according to data from the Jakarta Cancer Registry. Most breast cancer patients who present for treatment in Indonesia are in advanced stages of the disease, with 63% in stages III and IV at the time of diagnosis [3].

The relationship between increased platelet count and cancer stage has been well established. Thrombocytosis (i.e., a platelet count of more than 400,000/ μ L) has been found in various solid tumors, such as lung, kidney, breast, esophageal, stomach, and colon cancers. The prevalence of thrombocytosis varies from 10% to 57% in cancer patients [4]. The pathogenesis of thrombocytosis in malignancy is uncertain. However, there is evidence that tumor cells secrete humoral factors that can cause thrombocytosis [4,5]. Preoperative thrombocytosis has also been observed as a poor prognostic variable in gynecologic malignancies, including vulvar, cervical, ovarian, and endometrial cancers [6,7].

In breast cancer, thrombocytosis can occur due to the production of thrombopoietin, which stimulates platelet formation and is regulated by positive feedback from the granular alpha platelet content released during activation. Cancer cells can also produce thrombopoietin, especially in advanced cancers. Another theory suggests that the high involvement of interleukin 6 (IL-6) in the blood in the presence of malignancy also

*Corresponding author: Elridho Sampepajung, Division of Oncology, Department of Surgery, Faculty of Medicine, Hasanuddin University, Jalan Perintis Kemerdekaan KM 11, Makassar 90245, Indonesia. Fax: +62411585984; E-mail: elridhosampepajung@gmail.com; ORCID: <https://orcid.org/0000-0002-8247-0457> (P. Prihantono); <https://orcid.org/0000-0002-9236-0008> (N. Mariana); <https://orcid.org/0000-0002-7079-4585> (M. Faruk).

affects thrombocytosis [4]. Tanaka et al. reported the involvement of IL-6 in hematopoiesis and the inflammatory response. IL-6, thrombopoietin, and a combination of the two may be associated with participation in cancer cell-induced thrombocytosis [8].

An increased risk of thrombocytosis has been observed for many years in patients with breast cancer, although until recently it was considered to be a paraneoplastic phenomenon; women with breast cancer and thrombocytosis tend to have a poor prognosis, which is believed to have a direct role in its pathogenesis [9,10]. This is consistent with the role of platelets in inflammation, wound healing, and sepsis, and current clinical and experimental evidence suggest a role in breast cancer progression [7,9,10].

A complete blood-count examination, which includes the platelet index, is a simple, fast, and inexpensive clinical methodology. To our knowledge, there has been no published research on the correlation between platelet counts and breast cancer in Indonesia. The current study therefore examined this relationship.

2. Methods

This cross-sectional study was approved by the local institutional review board (No: 212/UN4.6.4.5.31/PP36/2021). The study population comprised breast cancer patients presenting at Dr. Wahidin Sudirohusodo Makara between February 2020 and January 2021. We collected data from the medical records of 171 breast cancer patients. The research sample included secondary data obtained from observations recorded in the medical records of breast cancer patients accompanied by the first platelet examination before breast cancer therapy and the staging examinations based on the TNM classification according to the American Joint Committee on Cancer (AJCC) 8th Edition. The inclusion criteria were no history of chemotherapy or radiation, and histopathologically diagnosed breast cancer according to biopsy. The exclusion criteria were a history of severe comorbid diseases (such as bleeding disorders, liver diseases, and immune-compromising diseases), incomplete medical record data, and blood tests that were not representative or not performed at our institution.

2.1. Breast cancer stages

The size of the primary tumor and the presence of regional lymphadenopathy and distant metastases determined the overall anatomic stage, which ranged

from stage 0 to stage IV according to the AJCC 8th Edition [11–13]. *In situ* breast cancer was defined as not having spread beyond the duct or lobule where it began (non-invasive) and was classified as stage 0. Early-stage breast cancer was defined as a tumor that was less than 5 cm in diameter and that had not spread to more than three lymph nodes, which was classified as phases IA, IB, and IIA. Locally advanced breast cancer was defined as a tumor that was more than 5 cm in diameter, where the malignancy had progressed to the skin, chest wall muscles, or more than three lymph nodes, and was classified as stages IIB, IIA, IIB, and IIIC, which included inflammatory breast cancer. Advanced breast cancer was defined as having spread to other parts of the body and was classified as stage IV.

2.2. Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc.) and the Kolmogorov–Smirnov test was used to assess whether variables (age and platelets) were normally distributed. The Chi-squared test was used to determine whether the data were evenly distributed. The Kruskal–Wallis test was applied to assess whether there was a difference in the number of platelets according to the stage; if a difference was detected, a post hoc follow-up test was carried out to assess which stage was significantly different. Results were considered statistically significant at $p < 0.05$.

3. Results

This study was conducted on 171 breast cancer patients of varying ages ranging from 21 to 73 years (Table 1).

Table 2 illustrates that the platelet data were not normally distributed according to the Shapiro–Wilk test (sig. < 0.05). Whereas there was a normal distribution for the age data. Because the platelet data were not normally distributed, the Kruskal–Wallis test was used to determine whether there was a difference in platelet count based on stage.

Table 3 shows that five patients had metastasis (2.92%), whereas 166 patients (97.8%) did not. The mean age of the non-metastatic patients was 46.94 ± 8.188 years, and that of the patients with metastasis was 41.20 ± 6.686 years. The mean platelet count in non-metastatic patients was 352.69 ± 158.636 and that in metastatic patients was 342.80 ± 94.182 .

Table 1
Patient characteristics

No.	Stage	Number of patients	%	Average platelet count (mm ³ /l)	Average age (years)	Metastasis
1	Stage 1	1	0.5	241.00	39.00	–
2	Stage 2a	4	2.34	369.75	51.25	–
3	Stage 2b	5	2.92	316.00	59.00	–
4	Stage 3a	59	34.50	318.00	45.92	–
5	Stage 3b	24	14.04	342.04	47.00	–
6	Stage 3c	73	42.69	347.59	47.34	–
7	Stage 4	5	2.92	342.80	41.20	5

Table 2
Normality test

	Kolmogorov–Smirnov ^a			Shapiro–Wilk		
	Statistics	Df	Sig.	Statistics	Df	Sig.
Age	0.058	171	0.200*	0.988	171	0.167
Platelets	0.177	171	0.000	0.851	171	0.000

*Lower bound of the true significance. ^aLilliefors significance correction.

Table 3

Characteristics of breast cancer patients based on age, platelets, and presence or absence of metastasis

	Metastasis	N (%)	Mean	SD
Age	Yes	166 (97.8)	46.94	8.188
	No	5 (2.92)	41.20	6.686
Platelets	Yes	166 (97.8)	352.69	158.636
	No	5 (2.92)	342.80	94.182

Table 4 shows that the relative numbers of patients in each group were 10 (5.85%) for the early stage, 156 (91.23%) for the locally advanced stage, and five (2.92%) for the advanced stage. The mean age of patients at the early stage was 49.90 ± 9.92 years, at the locally advanced stage was 46.75 ± 8.096 years, and at the advanced stage was 41.20 ± 6.686 years.

Table 5 shows that the early-stage group comprised 10 patients (5.85%), the locally advanced stage comprised 156 patients (91.23%), and the advanced stage comprised five patients (2.92%). The mean platelet counts were 330.00 ± 76.716 mm³/l at the early stage, 354.14 ± 162.518 mm³/l at the locally advanced stage, and 342.80 ± 94.182 mm³/l at the advanced stage.

Table 6 shows that there were no statistically significant differences among the three staging groups based on the platelet count ($p = 0.952$).

4. Discussion

Data were collected from 171 patients diagnosed with breast cancer in various staging groups and with differing platelet counts. The age distribution indicated that the majority of the patients with early stage breast cancer in this sample were in the younger age groups. Five (2.92%) of the patients had metastases and 166 (97.8%) did not.

A comparison of the platelet counts showed no statistically significant differences between the three staging groups ($p = 0.952$). This contradicted research by Takeuchi et al. that examined the prognostic impact of platelets on breast cancer and reported that activated platelets promoted tumor-cell growth, angiogenesis, and invasion. Platelet activity was previously inferred the platelet volume index (PVI), which included the platelet distribution width (PDW), mean platelet volume (MPV), platelet-distribution width/platelet-count ratio (PDW/P), and average platelet volume:platelet count ratio, retrospectively, in a study of 275 patients with breast cancer. PVI was compared with clinicopathological variables and assessed to identify independent indicators associated with disease-free survival (DFS). The increase in PDW/P was significantly correlated with age and human epidermal growth factor receptor-2 (HER2) status. In multivariate analysis, large tumor size and increased PDW/P were significant prognostic factors for DFS [14]. Elyasinia et al. showed that significantly higher platelet counts were associated with higher levels of staging [15]. This contradicted research by Huang et al. suggesting that an increase in

Table 4
Characteristics of breast cancer patients based on age, platelets, and stage

	Stage	N (%)	Mean	Standard deviation (SD)
Age	Early	10 (5.85)	49.90	9.492
	Locally advanced	156 (91.23)	46.75	8.096
	Advanced	5 (2.92)	41.20	6.686
Platelets	Early	10 (5.85)	330.00	76.716
	Locally advanced	156 (91.23)	354.14	162.518
	Advanced	5 (2.92)	342.80	94.182

Table 5
Descriptive statistical values of stage grouping

	Stage	n	Mean	SD	%
Platelets	Early	10	330.00	76.716	5.85
	Locally advanced	156	354.14	162.518	91.23
	Advanced	5	342.80	94.182	2.92

PDW might serve as a marker of poor prognosis in breast cancer [16].

A high platelet count is thought to be associated with breast cancer metastases. Platelets can promote tumor angiogenesis and stromal formation by secreting vascular endothelial growth factors and facilitating inflammatory cell migration [17]. Preoperative elevated platelet counts have been identified as a poor prognostic indicator of bronchial, gastric, and gynecologic malignancies. A high platelet count has been associated with tumor progression and poor survival in patients with esophageal cancer [18]. Platelets have been implicated in the mechanisms leading to carcinogenesis, tumor growth, angiogenesis, and tumor metastasis, as well as therapeutic outcomes. An increased platelet count has been associated with a poor prognosis in a broad spectrum of malignancies, such as pancreatic, gastric, colorectal, endometrial, and ovarian cancers. The balance of the production level determines the number of platelets compared to their use. An average platelet count cannot be interpreted as a hypercoagulable and pro-inflammatory state in the presence of an efficient compensatory mechanism [16].

The peripheral blood count is an initial routine examination performed in patients before surgery. Because there is a strong relationship between cancer and the body's immune response, clinical staging at presentation and altered hematological parameters can influence disease progression and vice versa. Rana et

al. reported a case control study of 50 patients (35 with malignant breast cancers and 15 controls with benign breast cancers). Clinical staging was performed and correlated with complete blood count according to the TNM classification. They found a significant correlation between absolute lymphocyte count and TNM staging. The mean platelet count for malignant breast cancer (291.51 ± 103.38) was higher than that for the benign group (222.82 ± 57.62). Preoperative thrombocytosis has been identified as a poor prognostic indicator in some malignancies. Another study of patients with esophageal carcinoma showed that high platelet counts were associated with tumor progression and poor survival [19]. Akinbami et al. also showed that the pre-chemotherapy platelet count of 291.51 ± 103.38 was higher than that of healthy controls (222.82 ± 57.62) [18].

Further studies are required using indicators such as the platelet-lymphocyte ratio (PLR) or the platelet distribution width-to-platelet count ratio (PDW/P). The PLR is a readily available biomarker for the management of breast cancer [17]. The PDW/P is also simple, relatively inexpensive, and almost universally available using routine blood counts, which makes it an attractive biomarker for breast cancer-risk assessment [14].

Table 6
Kruskal–Wallis test

	Group	n	Mean rank	Chi-squared	Df	Asymp. Sig.
Platelets	Early	10	84.25	0.099	2	0.952
	Locally advanced	156	85.90			
	Advanced	5	92.50			

5. Conclusion

There was no significant relationship between increased platelet count and TNM staging in breast cancer patients in this study. However, an increased platelet value was correlated with staging and prognosis in previous studies.

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