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A Comparative Analysis of Laboratory Parameters across Various Stages of Breast Cancer at a Tertiary-Level Hospital in Indonesia

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ABSTRACT

Background and Objective: Breast cancer has a high incidence and an unfavorable rate of delayed diagnosis. Previous studies have demonstrated that laboratory evaluations can aid in the monitoring and prognostic assessment of breast cancer patients. The purpose of this study was to evaluate the value of laboratory parameters across different stages of breast cancer at an Indonesian tertiary-level hospital.

Methods: This cross-sectional study was conducted on 159 breast cancer patients (including both inpatients and outpatients) who were selected through consecutive sampling from among those referred to the hospital. The required data were extracted and collected from the electronic medical records archive and case-mix data. The patients were divided into three groups based on clinical stage (stages II, III, and IV); no patients were classified as stage I. Hematological, hemostatic, and serological variables were examined and compared across the different groups.

Findings: Based on the findings of this study, statistically significant differences were observed in the values of the investigated parameters across different stages of breast cancer, including red blood cell count ($p=0.020$), prothrombin time (PT) ($p=0.007$), and the tumor marker CA 15-3 ($p<0.001$). In post-hoc analysis, red blood cell count showed a significant difference between stage III and stage IV patients ($p=0.027$). Furthermore, prothrombin time and CA 15-3 demonstrated statistically significant differences between stages II and IV patients ($p=0.030$ and $p<0.001$, respectively) as well as between stages III and IV patients ($p=0.027$ and $p=0.002$, respectively).

Conclusion: The results of this study demonstrated that red blood cell count, prothrombin time, and CA 15-3 levels exhibited significant differences between breast cancer patients in stages III and IV. Furthermore, CA 15-3 and prothrombin time values were significantly higher in stage IV patients compared to those in stages II and III, suggesting the potential value of these parameters in distinguishing advanced disease stages.

Keywords: *Breast Cancer, Clinical Laboratory, Hematology, Hemostasis, Malignancy, Tumor Marker.*

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Introduction

Breast cancer (BC) is a malignant condition arising in breast cells. It is the second most common cause of cancer-related deaths, surpassed only by lung cancer, and has become the most prevalent cancer type in women (1). In Indonesia, it accounted for 19.2% of all cancer cases (2). Data from the Global Cancer Observatory (GLOBOCAN) 2020 revealed that new cancer cases in Indonesia reached 396,914, of which 16.6% (68,858) were BC (1). This underscores the position of BC as the most frequent malignancy in Indonesia (1, 3). In diagnosing oncological diseases, laboratory diagnosis along with additional examinations is performed. Laboratory tests such as blood chemistry tests, hematology, serology, tumor markers, and urinalysis are commonly used in cancer diagnosis (4-6). Laboratory testing has immense potential as a means of early detection, particularly for BC (7). Furthermore, it can aid in assessing therapeutic response and patient prognosis (8-10). Analyzing these findings, especially in the early cancer stages, can help predict cancer metastasis.

In patients with BC, hematological abnormalities are frequently observed (11). As demonstrated in a previous study, patients with advanced BC (stage T3 and T4) exhibit a higher proportion of anemia compared with those with early-stage BC (T0-T2), with proportions of 84% and 16%, respectively. This finding may be associated with hemolysis, decreased production, or blood loss (12). Anemia may develop as a result of hemolysis, suppression of hematopoiesis, or blood loss (13). Patients may also commonly present with hemostatic dysregulation, including systemic hypercoagulability. However, findings in the literature are often contradictory; one previous study reported that coagulation parameters—including prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer—are comparable across BC stages (14). In contrast, another study determined that in patients with advanced and progressive BC, abnormalities in routine coagulation tests are the norm, particularly manifesting as elevated D-dimer levels and reduced platelet counts (15). Identifying these abnormalities may help elucidate the biological etiologies underlying these conditions, as well as how hemostatic elements may contribute to metastatic potential in BC (16, 17).

Other laboratory parameters that may be assessed include liver function tests, specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These tests can be performed in patients with advanced-stage disease to detect liver metastasis (9). Another study also reported that elevation of alkaline phosphatase (ALP) is more common in advanced-stage BC than in early-stage BC (59% vs. 41%), and this elevation may serve as a predictor of bone and liver metastasis. In addition, urea elevation, which can serve as an indicator of renal function, is observed more frequently in patients with advanced BC (12). The monitoring of lactate dehydrogenase (LDH) levels constitutes a standard, accessible, and low-cost prognostic indicator for BC, given that LDH levels are elevated in malignant states (18). Meanwhile, tumor markers may also be used for disease monitoring. Patients with BC are routinely evaluated for cancer antigen 15-3 (CA 15-3), a glycoprotein that is overexpressed in malignancy and can assist in detecting disease progression (19).

The disparity in cancer mortality rates between developing nations, such as Indonesia, and high-income countries is considerable. Available data indicate that delayed diagnosis represents a significant contributing factor to these elevated statistics (20). Furthermore, the scarcity of studies conducted on this topic has also contributed to this phenomenon. This point is particularly important to emphasize, given that metastatic disease is widely regarded as a major clinical obstacle and is responsible for the majority of cancer-related

fatalities (21). Therefore, the present study was undertaken to evaluate the characteristics of various laboratory parameters according to distinct BC stages, with the ultimate goal of identifying potential laboratory tests that can be routinely ordered to facilitate the detection of cancer progression.

Methods

The present investigation was conducted using a cross-sectional design, which permitted the simultaneous collection of all study variables. Participants were recruited by means of consecutive sampling, ensuring the inclusion of all individuals who satisfied the inclusion and exclusion criteria during the designated study timeframe. The current study collected secondary data from both inpatient and outpatient BC patients who received treatment at Dr. Mohammad Hoesin Hospital, Palembang, Indonesia, from 1 January 2018 to 31 December 2022. All data were retrieved from the case-mix and medical record unit. Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Sriwijaya University (approval number: 211-2023).

BC patients were clinically classified from stage I through stage IV. For the purposes of the present study, patients were divided into three groups—BC stage II, stage III, and stage IV—as no patients with BC stage I were available for inclusion. Patients were eligible for inclusion if their electronic medical record data were complete for the observed variables described below and if their first visit occurred within the analysis period. Patients with BC were excluded if they were pregnant or had other malignancies at the time of assessment.

Patients' ages were categorized into six classes: 18-25, 26-35, 36-45, 46-55, 56-64, and ≥65 years (22). Meanwhile, BC patients were classified into five histological subtypes: (1) ductal carcinoma in situ (DCIS), (2) lobular carcinoma in situ (LCIS), (3) invasive ductal carcinoma (IDC), (4) invasive lobular carcinoma (ILC), and (5) other types (23). Furthermore, laboratory parameters were classified into three main categories: (1) hematology (hemoglobin [Hb], red blood cell count [RBC], white blood cell count [WBC], neutrophils, platelets [PLT], mean platelet volume [MPV], and red cell distribution width [RDW]); (2) hemostasis (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen, and D-dimer); and (3) serology (lactate dehydrogenase [LDH], aspartate transaminase [AST], alanine transaminase [ALT], and cancer antigen 15-3 [CA 15-3]).

Descriptive analysis was carried out to determine the characteristics of patients with BC with respect to age, sex, histological classification, and disease stage. Inferential analysis was then performed to compare laboratory results across BC stages using either one-way analysis of variance (ANOVA) or the Kruskal–Wallis tests, based on data distribution. When statistically significant results were identified, post-hoc analysis was conducted to determine which specific BC stages differed significantly from the others. Post-hoc tests were performed using either the Tukey test for parametric data or the Bonferroni correction for non-parametric data. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp). A p-value of less than 0.05 was considered statistically significant.

Results

The present study comprised 159 samples, with 43, 54, and 62 samples representing BC stages II, III, and IV, respectively. The majority of participants were female, comprising 154 individuals (96.86%) of the

total population. The largest proportion of samples (36.49%) was obtained from patients aged between 46 and 55 years, with an overall mean age of 48.63±10.26 years (similar across BC stages). With regard to histological subtypes, no LCIS samples were obtained. In addition, no DCIS samples were identified among stage III or stage IV BC cases. IDC was the most prevalent BC subtype, accounting for 65.41% of the samples. ILC was most frequently identified in patients with stage IV BC. The data are presented in Table 1.

With respect to laboratory assessment, hemoglobin (p=0.090), WBC (p=0.265), neutrophils (p=0.166), PLT (p=0.841), MPV (p=0.203), RDW (p=0.109), aPTT (p=0.459), fibrinogen (p=0.920), D-dimer (p=0.950), LDH (p=0.973), AST (p=0.594), and ALT (p=0.664) levels were comparable across BC stages. In contrast, RBC (p=0.020), PT (p=0.007), and CA 15-3 (p<0.001) values exhibited statistically significant differences between BC stages. Complete details of the laboratory results are presented in Table 2. The post-hoc analysis revealed that statistically significant differences in laboratory parameters were detected between stage III and stage IV BC for the following parameters: RBC (p=0.027, Tukey test), PT (p=0.020, Bonferroni correction), and CA 15-3 (p=0.004, Bonferroni correction). Furthermore, when comparing stage II and stage IV BC, significant differences were observed for PT (p=0.021, Bonferroni correction) and the tumor marker CA 15-3 (p<0.001, Bonferroni correction).

Table 1. Gender, age, and histological classification between breast cancer stages

Variables	Total (n=159) Number(%)	Stage II (n=43) Number(%)	Stage III (n=54) Number(%)	Stage IV (n=62) Number(%)
Gender				
Male	5(3.14)	1(2.33)	3(5.55)	1(1.61)
Female	154(96.86)	42(97.67)	51(94.45)	61(98.39)
Age (Years)	48.63±10.26	48.30±9.63	48.67±10.00	48.82±11.04
18-25	0(0.00)	0(0.00)	0(0.00)	0(0.00)
26-35	14(8.81)	2(4.65)	5(9.26)	7(11.29)
36-45	48(30.19)	15(34.88)	18(33.33)	15(24.19)
46-55	58(36.49)	15(34.88)	21(38.89)	22(35.49)
56-64	29(18.25)	9(20.94)	5(9.26)	15(24.19)
≥ 65	10(6.29)	2(4.65)	5(9.26)	3(4.84)
Histological classification				
DCIS	2(1.26)	2(4.65)	N/A	N/A
LCIS	0(0.00)	0(0.00)	N/A	N/A
IDC	104(65.41)	34(79.07)	39(72.23)	31(50)
ILC	8(5.03)	2(4.65)	2(3.70)	4(6.45)
Other types	45(28.30)	5(11.63)	13(24.07)	27(43.55)

Note: N/A= Not Available

Abbreviations: DCIS= Ductal Carcinoma in Situ, IDC= Invasive Ductal Carcinoma, ILC= Invasive Lobular Carcinoma, LCIS= Lobular Carcinoma in Situ

Table 2. Laboratory results corresponding to breast cancer stages

Variables	Total n=159	Stage II n= 43(27.04)	Stage III n= 54(33.96)	Stage IV n= 62(40)	p-value
Hematology					
Hb(g/dL)	11.37±1.9	11.77±1.82	11.50±1.99	10.98±1.81	0.090[a]
RBC(10^6/ mm^3)	4.0±0.66	4.15±0.70	4.19±0.57	3.87±0.68	**0.020[a]**
WBC(10^3/ mm^3)	7.8 (0.74-49.2)	7.33 (3.2-49.2)	8.15 (4.2-22.0)	8.75 (0.74-27.3)	0.845[a]
Neutrophil(%)	60 (10-94)	58 (41-88)	59 (11-90)	63 (10-94)	0.462[a]
PLT(10^3/µL)	333 (13-839)	323 (13-839)	333.5 (106-821)	341.5 (18-696)	0.723[a]
MPV(fL)	9.6 (7.7-64) n=153	9.5 (7.8-56) n=41	9.8 (7.7-64) n=52	9.5 (7.9-11.8) n=60	0.448[a]
RDW(%)	14.1 (11.5-42.1) n=158	14 (11.5-19) n=42	13.85 (11.6-28.5)	14.5 (11.9-42.1)	0.109[b]
Hemostasis					
PT (seconds)	13.8 (11.4-30.8) n=70	13.45 (12.6-25.2) n=14	13.50 (11.5-23.1) n=19	14.7 (11.4-30.8) n=37	**0.007[b]**
aPTT (seconds)	28.8 (20.4-63.7) n=70	30.25 (20.4-39.8) n=14	28.6 (22.2-46.1) n=19	28.7 (21.8-63.7) n=37	0.459[b]
Fibrinogen (mg/dL)	442.76±139.82, n=38	440±172.18, n=5	462.71±196.67, n=7	437.92±121.14 n=26	0.920[a]
D-dimer (ng/mL)	2.78 (0.22-19.06) n=37	4,88 (0.22-7.4) n=5	1.95 (0.58-16.31) n=6	2.99 (0.27-19.06) n=25	0.950[b]
Serology					
LDH (U/L)	306 (147-2979) n=38	390 (153-410) n=3	327 (159-507) n=5	299 (147-2979) n=30	0.795[a]
AST (U/L)	32 (10-905) n=74	29 (13-106) n=13	27.5 (19-533) n=16	34 (10-905) n=45	0.594[b]
ALT (U/L)	22.5 (6-167) n=72	18 (6-77) n=13	24.5 (10-80) n=16	24 (7-167) n=43	0.604[a]
Ca 15-3 (U/mL)	24.2 (4.5-7202) n=83	13.8 (4.5-116.7) n=20	16 (6.5-1157.8) n=22	47.3 (7.7-7202) n=41	**<0.001[b]**

Note: P-value<0.05 based on [a]One-way analysis of variance (ANOVA) and [b]Kruskal-Wallis tests

Abbreviations: ALT= Alanine Aminotransferase, aPTT= Activated Partial Thromboplastin Time, AST= Aspartate Aminotransferase, Ca 15-3= Cancer Antigen 15-3, Hb= Hemoglobin, LDH= Lactate Dehydrogenase, MPV= Mean Platelet Volume, PLT= Platelets, PT= Prothrombin Time, RBC= Red Blood Cell, RDW= Red Cell Distribution Width, WBC= White Blood Cell

Discussion

The present study aimed to evaluate the differences in laboratory parameter values across the various stages of BC. Following a comprehensive assessment of hematological, hemostatic, and serological parameters, only three variables—namely RBC, PT, and CA 15-3—were found to demonstrate statistically significant findings. In contrast, the remaining laboratory variables exhibited relatively similar values across the different BC stages.

With respect to sample characteristics, the majority of participants were female, accounting for 96.86% of the entire cohort. This finding is consistent with the high female-to-male ratio observed in BC, particularly among individuals aged over 45 years (24, 25), which may be associated with enhanced hormonal stimulation by estrogen and progesterone in females relative to males (26). Estrogen receptors are present in mammary cells, permitting activation and stimulation of abnormal cell proliferation (27). This is associated with an increased risk of BC in both premenopausal and postmenopausal women (28). However, it is noteworthy that the proportion of male BC cases in our cohort exceeded commonly reported figures, comprising more than 3% of cases, whereas international statistics indicate that only approximately 1% of BC cases and mortalities occur in men (25). This phenomenon may be associated with an increased prevalence of BC-related risk factors, including obesity, smoking, and diabetes, within the observed population (29-31).

The incidence and prevalence of BC increase with advancing age. This trend is associated with the accumulation of cellular injury over time, increased exposure to carcinogens, and enhanced carcinogenesis (32). Mutations and genetic instabilities are significant contributors to cancer development, along with deficiencies in DNA repair mechanisms (33, 34). These processes are also linked to telomere degradation, which leads to a diminished capacity for DNA repair as a consequence of the aging process (35). With regard to BC specifically, approximately 80% of cases occur in women aged over 50 years (36). The disease is less common in younger populations but tends to exhibit a more aggressive clinical course (36). However, in the current study, the mean age of BC patients was less than 50 years (approximately 48 years). This is lower than the average reported in several countries, including the United States, Japan, and Korea (37, 38). This phenomenon has been a matter of concern in relation to the high prevalence of young-onset BC compared with Western countries, particularly since the underlying reasons for these discrepancies have not been clearly elucidated (38).

No LCIS subtype was found in this study. This is consistent with data indicating that this subtype is quite uncommon, comprising no more than 3% of the entire population (39). IDC is the most common BC type, whereas ILC usually accounts for around 5-15% of the population (39), similar to the findings of this study. Hemoglobin values were similar between BC stages, whereas RBC was significantly different between BC stages III and IV ($p=0.027$). A previous study found that the mean hemoglobin level and erythrocyte count were inversely related to the stage of BC (8). This is a sign of anemia of chronic illness, associated with a prolonged state of inflammation and release of proinflammatory cytokines (IL-1, IL-2, IL-6, and TNF-α) (40) during BC, which directly disrupts erythropoiesis in the bone marrow (41, 42).

The median values of leukocytes, neutrophils, and thrombocytes were slightly elevated as cancer stages advanced; however, these differences did not reach statistical significance. Another study reported a contrasting finding, demonstrating lower leukocyte counts as cancer progressed (43). In contrast, Al-Arifi et al. (44) reported results similar to ours, with elevated neutrophil counts. These observations may indicate multiple underlying conditions, such as bacterial infections or the release of cytokines during tumor invasion and metastasis (45).

Prolonged PT is observed in conjunction with cancer progression. The present study identified a significant difference in PT between stage II vs. IV and stage III vs. IV BC. This finding differs from a previously reported study that demonstrated a U-shaped trend, with the longest PT observed in stage I and stage IV BC (46). However, PT-international normalized ratio (PT-INR) and PT were positively associated with in-hospital mortality (OR=1.62 and 1.08, respectively) (47). Meanwhile, aPTT, fibrinogen, and D-dimer levels did not exhibit statistically significant differences across BC stages. Nevertheless, this may be attributed to the small number of stage II and III BC patients who underwent hemostatic testing, given that these tests are not routinely indicated in earlier BC stages (48). Assuming normal fibrinogen levels, prolonged PT and aPTT indicate a deficiency in coagulation factors (49). Patients with BC are susceptible to coagulation disorders, which are associated with activation of the coagulation cascade by the tumor (15). Furthermore, angiogenesis stimulated by tumor cells through the release of vascular endothelial growth factor (VEGF)-A may create neovasculature that is defective in both function and morphology (50).

CA 15-3 levels increased significantly in stage IV BC. This finding is based on the results of the present study, which demonstrated significantly elevated levels of this biomarker between stage II vs. IV and stage III vs. IV BC. CA 15-3 may be utilized as an indicator of BC progression toward advanced stages (51). Furthermore, treatment, tumor size, positive axillary lymph node status, and cell subtype may influence CA 15-3 levels (52). Overexpression of mucin-1 (MUC-1) in malignant cells also contributes to increased CA 15-3 levels (53).

Several limitations of this investigation should be acknowledged, including factors that may influence the interpretation of laboratory values, such as the presence of comorbidities and unrecorded medication usage, neither of which was accounted for in this study. Furthermore, the sample size for various laboratory tests was limited in specific stages, particularly for hemostasis and serology assessments. Additionally, information regarding the histological subtype of BC was not documented beyond ILC, IDC, LCIS, and DCIS, resulting in a high percentage of unclassified subtypes.

The present study documented statistically significant differences in laboratory parameters across cancer stages for RBC ($p=0.020$), PT ($p=0.007$), and CA 15-3 ($p<0.001$) values. RBC count was found to differ significantly between stages III and IV ($p=0.027$). Prothrombin time differed significantly between stages II and IV ($p=0.030$) and between stages III and IV ($p=0.027$). Meanwhile, CA 15-3 values differed significantly between stages II and IV ($p<0.001$) and between stages III and IV ($p=0.002$). Based on these findings, routine examination of hematological, hemostatic, and tumor markers may be utilized for the early detection and prediction of BC stage.

Competing interests: The authors declare that they have no competing interests.

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