Original article

Clinical significance of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in breast cancer according to immunohistochemical subtypes and disease stage

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Received: 29/12/2025; **Accepted:** 12/03/2026; **Published:** 30/04/2026
DOI: 10.34071/jmp.2026.2.869

Abstract

Background: Systemic inflammation plays a pivotal role in breast cancer (BC) progression and has been increasingly recognized as an important component associated with tumor aggressiveness. Inflammatory indices derived from routine blood tests, particularly the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), reflect the balance between tumor-promoting inflammatory responses and host antitumor immune surveillance.

Objectives: To evaluate changes in systemic inflammatory markers in BC patients compared with healthy controls and to analyze their associations with TNM stage and immunohistochemical (IHC) subtypes.

Methods: A descriptive cross-sectional study was conducted at Hue University of Medicine and Pharmacy Hospital, enrolling 30 newly diagnosed, untreated female BC patients and 35 healthy women. Clinical characteristics, TNM staging, and immunohistochemical (IHC) profiles (ER, PR, HER2, Ki-67) were collected. Patients were classified into early-stage (TNM I–IIA) and late-stage disease (TNM IIB–IV). Based on IHC profiles, tumors were categorized into Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC), with Luminal A considered low-risk and non-Luminal A subtypes considered higher-risk. NLR and PLR were calculated from peripheral blood counts and compared between groups, across disease stages, and IHC-based risk categories.

Results: BC patients exhibited significantly higher NLR and PLR than controls ($P < 0.05$). Both indices were significantly elevated in BC patients with advanced-stage (IIB–IV) compared with early-stage (I–IIA) ($P < 0.05$). Patients with high-risk IHC subtypes, particularly non-Luminal A tumors, showed significantly higher NLR levels than those with Luminal A tumors ($P < 0.05$). In contrast, conventional tumor markers, including CEA, CA 15-3, and C-reactive protein, did not show statistically significant differences across TNM stages or IHC subtypes.

Conclusion: NLR and PLR are closely associated with disease stage and immunohistochemical subtypes in breast cancer. As simple, low-cost, and readily available parameters, these indices may provide complementary information to conventional markers for initial risk stratification and clinical assessment in breast cancer patients.

Keywords: *Breast cancer; Systemic inflammation; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; TNM stage; Immunohistochemistry*

1. INTRODUCTION

Breast cancer (BC) is the most common malignancy and one of the leading causes of cancer-related mortality among women worldwide [1,2]. Increasing evidence has shown that systemic inflammation plays a crucial role in tumor development, invasion, and metastasis through its effects on the tumor microenvironment. In this context, inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as simple, inexpensive, and easily accessible biomarkers for cancer. These indices reflect the balance between tumor-promoting inflammatory responses and the host's anti-tumor immune surveillance capacity [2,3].

Numerous international studies have confirmed the prognostic relevance of NLR and PLR in BC. A large meta-analysis by Gu et al. (2024), involving thousands of patients, demonstrated that elevated pretreatment NLR was significantly associated with poorer overall survival and disease-free survival across different BC subgroups [4]. This association has been partly explained by increased neutrophil levels contributing to an immunosuppressive tumor

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microenvironment, thereby facilitating tumor cell escape from cytotoxic T-lymphocyte-mediated immune surveillance. In addition, PLR has also been shown to have prognostic value. Zhu et al. (2023) reported that PLR correlated with tumor burden, including tumor size and lymph node involvement, and served as a useful indicator for treatment response, particularly in patients receiving neoadjuvant chemotherapy [5]. More recently, Huang et al. (2025) highlighted that combining NLR and PLR with immunohistochemical subtypes, such as HER2-negative status, may improve the accuracy of predicting treatment resistance in breast cancer [9].

In developing countries, the clinical relevance of NLR and PLR is further emphasized by their high feasibility. These indices can be rapidly obtained from routine peripheral blood counts at low cost, providing additional information for patient evaluation at hospital admission. In clinical practice, BC is commonly classified according to TNM staging into early and late stages, as well as into distinct immunohistochemical subtypes that reflect tumor biology and aggressiveness. However, data linking systemic inflammatory markers with TNM stage and immunohistochemical subgroups in Vietnamese BC patients remain limited. Therefore, this study was conducted with the following objectives: (1) to evaluate changes in systemic inflammatory markers (NLR and PLR) in BC patients compared with healthy controls, and (2) to analyze the association between these markers and TNM staging as well as immunohistochemical subtypes.

2. METHODS

2.1. Study design and participants

This descriptive cross-sectional study was conducted at Hue University of Medicine and Pharmacy Hospital. The study included 30 female patients who were newly diagnosed with breast cancer and had not received any treatment before enrollment. A control group of 35 age-matched healthy women was recruited for comparison.

Inclusion criteria for BC patients were female patients aged 18 years or older, with a histopathological test confirmed diagnosis of primary breast cancer, complete TNM staging at diagnosis, and available immunohistochemical data, including ER, PR, HER2 status, and Ki-67 index. All patients were untreated at the time of blood sample collection. Exclusion criteria included patients with acute or chronic inflammatory diseases, active infections, autoimmune disorders, hematological diseases, severe liver or renal dysfunction, other malignancies, or those using corticosteroids, immunosuppressive, or anti-inflammatory drugs at the time of blood sampling, or those who declined to participate in the study. The healthy control group consisted of women without a history of cancer, inflammatory or autoimmune diseases, chronic systemic disorders, or current infections, and with normal findings on routine clinical examination.

2.2. Clinical and immunohistochemical data collection

Clinical data were collected from medical records, including age, TNM stage and IHC results at diagnosis. Tumor staging was determined according to the TNM classification system. Immunohistochemical analysis was performed on tumor tissue to determine ER, PR, HER2 status, and Ki-67 index. Based on IHC results, patients were classified into biological subtypes, including Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC).

2.3. Laboratory measurements

Peripheral blood samples were collected from all participants under fasting conditions. Routine hematological parameters, including neutrophil count, lymphocyte count, and platelet count, were measured using an automated hematology analyzer. Serum biochemical parameters, including cancer antigen 15-3 (CA 15-3), carcinoembryonic antigen (CEA), C-reactive protein (CRP), and glucose, were analyzed using standard laboratory methods.

2.4. Systemic inflammatory indices

The neutrophil-to-lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The platelet-to-lymphocyte ratio (PLR) was calculated as the absolute platelet count divided by the absolute lymphocyte count. These indices were used to evaluate systemic inflammatory status.

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation, whereas non-normally distributed variables were expressed as median (interquartile range - IQR), and categorical variables as numbers and percentages. Comparisons between two independent groups were conducted using the independent Student *t*-test for normally distributed data, while the Mann–Whitney U test was applied for non-normally distributed data or small sample sizes ($n \leq 10$). Data were visualized using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). A two-tailed *P*-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Clinical and laboratory characteristics of the study population

Table 1. Comparison of clinical and laboratory characteristics between healthy controls and breast cancer patients (mean ± SD)

Clinical parameters	Healthy controls (n = 35)	BC patients (n = 30)	*P* value
Age	51.29 ±13.00	53.93 ± 10.19	0.3702
Red blood cells ($\times 10^{12}$/L)	4.48 ± 0.26	4.33 ± 0.36	0.0560
Hemoglobin (g/L)	133.3 ± 7.58	125.4 ± 10.05	**0.0006**
White blood cells ($\times 10^{9}$/L)	6.85 ± 1.08	6.68 ± 1.28	0.5755
Neutrophils (%)	54.91 ± 7.06	56.99 ± 9.71	0.3221
Lymphocytes (%)	34.33 ± 5.87	29.76 ± 7.73	**0.0087**
Platelets ($\times 10^{9}$/L)	249.7 ± 55.26	268.8 ± 57.91	0.1794
Fast Blood Glucose (mmol/L)	5.02 ± 0.39	5.89 ± 1.95	0.0967

Note: *Data are presented as mean ± standard deviation (SD). Comparisons between the two groups were performed using an independent t-test. A P value < 0.05 was considered statistically significant. BC: breast cancer.*

Table 1 presents the comparison of clinical and laboratory characteristics between the healthy control group and breast cancer patients. Hemoglobin levels were significantly lower in the breast cancer group compared with controls (125.4 ± 10.05 g/L vs. 133.3 ± 7.58 g/L, *P* = 0.0006). In addition, the percentage of lymphocytes was significantly reduced in breast cancer patients (29.76 ± 7.73%) compared with the control group (34.33 ± 5.87%, *P* = 0.0087). Mean age and other hematological parameters, including red blood cell count, total white blood cell count, neutrophil percentage, platelet count, and fasting blood glucose levels, showed no significant differences between the two groups (*P* > 0.05).

Table 2. Distribution of TNM stages and immunohistochemical subtypes in breast cancer patients (n = 30)

Classification			n		%	
TNM	I, IIA	Early stage	10		33.3	
	IIB, III, IV	Late stage	20		66.7	
	Total		30		100	
Immuno-histochemistry (IHC)	Luminal A	Low risk	10		33.3	
	Luminal B	High risk (non – Luminal A)	9	20	30	66.7
	HER2		8		26.7	
	TNBC		3		10	
	Total		30		100	

Note: *TNM staging was classified according to the AJCC criteria (2017). TNBC: triple-negative breast cancer.*

Table 2 summarizes the distribution of tumor stage according to the TNM classification and immunohistochemical subtypes in breast cancer patients. Among 30 patients, late-stage disease (IIB, III, and IV) was more common than early-stage disease (I and IIA), accounting for 66.7% and 33.3%, respectively. Regarding immunohistochemical classification, Luminal A subtype has the proportion of 33.3%, while the non-Luminal A subtype, including the Luminal B, the HER2-positive and the triple-negative breast cancer (TNBC) subtype, accounted for (66.7%).

3.2. Comparison of tumor markers and inflammatory markers according to TNM stage and immunohistochemical subtype

Table 3. Comparison of tumor and inflammatory markers according to TNM stage and immunohistochemical subtype in breast cancer patients (median [IQR])

Marker	TNM stage			Immunohistochemical subtype		
	Early stage (TNM I/IIA) (n = 10)	Late stage (TNM IIB–IV) (n = 20)	*P* value	Low-risk subtype (Luminal A) (n = 10)	High-risk subtypes (non-Luminal A) (n = 20)	*P* value
CEA (ng/mL)	1.67 [0.95 - 3.36]	1.54 [1.11 - 2.92]	0.9899	1.67 [1.39 - 4.91]	1.47 [0.98 - 2.92]	0.2796
CA 15-3 (U/mL)	15.46 [8.57 - 17.30]	13.91 [8.38 - 19.43]	0.9764	16.10 [11.26 - 18.20]	13.66 [8.51 - 19.14]	0.6870
CRP (mg/L)	0.63 [0.6 - 11.42]	1.39 [0.64 - 9.32]	0.7033	2.80 [0.61 - 14.64]	1.34 [0.62 - 8.40]	0.8021

Note: *Data are presented as median [IQR]because of non-normal distribution. Early stage includes TNM stages I and IIA, while late stage includes stages IIB, III, and IV. Low-risk subtype includes Luminal A tumors; high-risk subtypes include Luminal B, HER2-positive, and triple-negative breast cancer (TNBC). Statistical comparisons were performed using Mann–Whitney U test. A P value < 0.05 was considered statistically significant.*

As shown in Table 3, serum levels of CEA, CA 15-3, and CRP did not differ significantly between early-stage and late-stage breast cancer patients (*P* > 0.05). Similarly, when patients were stratified by immunohistochemical risk groups, no significant differences were observed in CEA, CA 15-3, or CRP levels between the low-risk group (Luminal A) and the high-risk group (Luminal B, HER2-positive, and TNBC) (*P* > 0.05).

3.3. Changes in systemic inflammatory markers (NLR and PLR) in breast cancer patients

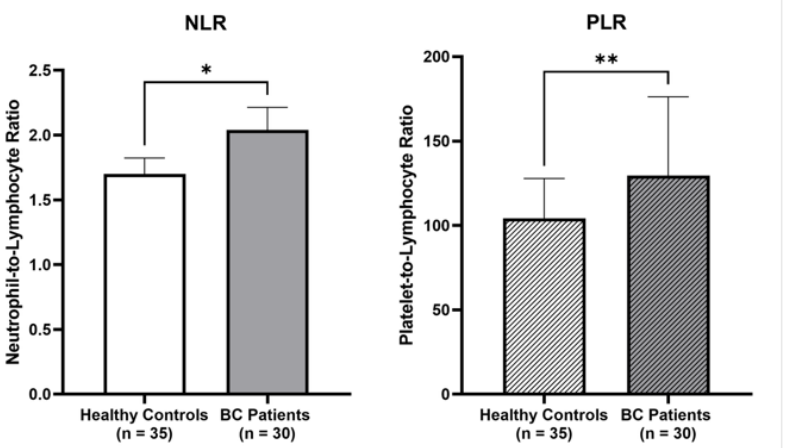

Figure 1. Comparison of systemic inflammatory markers (NLR and PLR) between healthy controls and BC patients

*Bar graphs show the mean ± SD of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in healthy controls and breast cancer patients. Statistical comparisons were performed using an independent t-test. *P < 0.05 indicates a statistically significant difference compared with the control group.*

As illustrated in Figure 1, the mean NLR value was significantly higher in breast cancer patients (2.13 ± 0.92) compared with healthy controls (1.68 ± 0.48, *P* = 0.042). Similarly, PLR was also significantly increased in the breast cancer group (148.5 ± 54.99) relative to controls (109.9 ± 27.72, *P* = 0.0034).

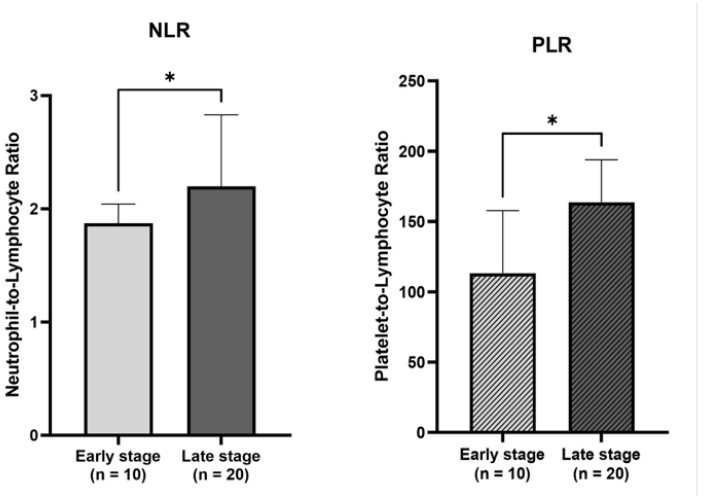

Figure 2. Comparison of systemic inflammatory markers (NLR and PLR) according to TNM stage in BC patients

*Bar graphs present mean ± SD values of NLR and PLR in early-stage (TNM I–IIA) and late-stage (TNM IIB–IV) breast cancer patients. Statistical analysis was conducted using Mann–Whitney U test. * P < 0.05 indicates a statistically significant difference.*

Figure 2 shows that both NLR and PLR were significantly higher in patients with late-stage breast cancer compared with those in early stages. Specifically, NLR increased from 1.58 ± 0.52 in early-stage patients to 2.41 ± 0.96 in late-stage patients (P = 0.0146). Similarly, PLR was higher in the late-stage group (161.4 ± 52.84) than in the early-stage group (122.9 ± 52.47, P = 0.0490).

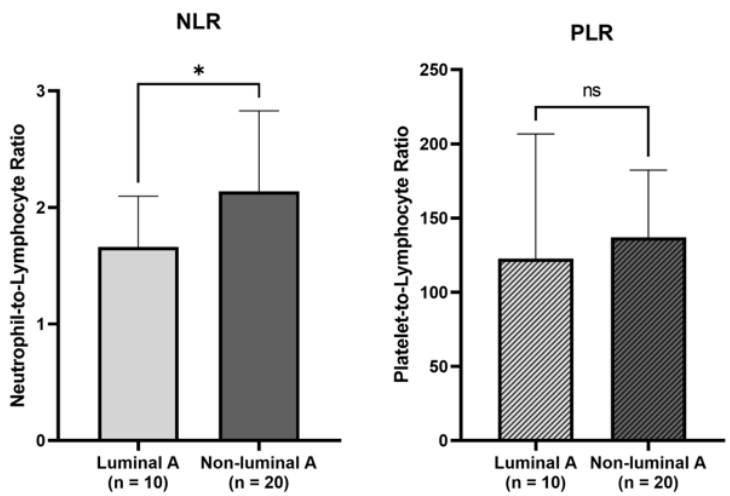

Figure 3. Comparison of systemic inflammatory markers (NLR and PLR) according to immunohistochemical subtypes in BC patients

*Bar graphs display mean ± SD values of NLR and PLR according to immunohistochemical risk groups. The low-risk group includes Luminal A tumors, while the non-Luminal A group, also known identified as the high-risk group, includes Luminal B, HER2-positive, and triple-negative breast cancer subtypes. Statistical analysis was conducted using Mann–Whitney U test. *P < 0.05 indicates a statistically significant difference.*

As shown in Figure 3, the mean NLR value was significantly higher in the high-risk immunohistochemical group (non-Luminal A group) (2.42 ± 0.05) compared with the Luminal A group (1.56 ± 0.54, P = 0.0167). Although PLR tended to be higher in the high-risk group (152.5 ± 52.68) than in the low-risk group (140.5 ± 61.48), this difference did not reach statistical significance (P = 0.5300).

4. DISCUSSION

Regarding the characteristics of our study subjects, we recorded a statistically significant decrease in hemoglobin concentration and lymphocyte percentage in the BC group compared to the control group ($P < 0.05$). Anemia and lymphopenia reflect a weakened anti-tumor immune surveillance system, which creates favorable conditions for malignant cells to escape inhibition and proliferate. In addition, the trend of increased blood glucose in the BC patient group (5.89 ± 1.95 mmol/L) recorded in our study is consistent with reports on the association between metabolic disorders and poor prognosis in cancer [6]. Within our study sample, the concentrations of CEA, CA 15-3, and CRP did not show statistically significant differences between early and late stages. This result aligns with several international [7] and Vietnamese studies [8] indicating that the value of CA 15-3 in screening and early diagnosis of breast cancer may not achieve high statistical significance, highlighting the necessity of integrating these biomarkers with imaging modalities and histopathological examination [10].

Notably, the systemic inflammatory markers NLR and PLR in BC patients compared to the control group in our study showed significant elevation ($P < 0.05$), with NLR at (2.13 ± 0.92) and PLR at (148.5 ± 54.99). This finding confirms the presence of a robust systemic inflammatory response triggered by the tumor. The NLR reflects an imbalance between the inflammatory response (increased neutrophils) and immune responsiveness (decreased lymphocytes). Similarly, the PLR suggests platelet proliferation and lymphopenia within the tumor microenvironment [10]. Both markers not only reflect the degree of inflammation but also indicate the body's impaired immune surveillance against cancer cells from the time of diagnosis. Studies in Vietnam have also begun focusing on this topic, identifying correlations between NLR/PLR and chemotherapy outcomes in BC patients [7], demonstrating the high clinical utility of these markers [11].

Furthermore, the relationship between systemic inflammatory markers (NLR, PLR) and TNM staging and immunohistochemical subtypes in our study holds significant practical value. Specifically, both NLR and PLR were significantly higher in the late stages (IIB, III, IV) compared to the early stages (I/IIA) ($P < 0.05$). This is consistent with recent international meta-analyses, confirming NLR and PLR as sensitive biomarkers for assessing tumor burden and metastatic potential [10]. A highlight of our study is the variation in NLR across biological subtypes. High-risk patient groups (Luminal B, HER2, TNBC) had a significantly higher mean NLR (2.42 ± 0.05) compared to the low-risk group (Luminal A) (1.56 ± 0.54, $P = 0.0379$). This suggests that systemic inflammation not only reflects the clinical stage but is also closely linked to the aggressive biological nature of tumor cells [4].

Several limitations should be acknowledged. First, the sample size was relatively small and the study was conducted at a single center, which may limit the generalizability of the findings. Second, the cross-sectional design did not allow assessment of changes in inflammatory markers over time or their association with clinical outcomes. Nevertheless, this study provides preliminary evidence on the relationship between systemic inflammatory markers and disease characteristics in breast cancer, highlighting the potential value of NLR and PLR as simple, cost-effective and readily available indicators in breast cancer context.

5. CONCLUSION

In summary, this study examined systemic inflammatory markers in breast cancer patients in relation to clinical stage and immunohistochemical subtypes. Breast cancer patients showed higher NLR and PLR values compared with healthy controls, reflecting an enhanced systemic inflammatory state. Both markers were significantly increased in patients with advanced TNM stages, suggesting a close association between systemic inflammation and tumor progression. In addition, higher NLR values were observed in high-risk immunohistochemical subtypes compared with Luminal A tumors, indicating a link between inflammatory status and more aggressive tumor biology. Taken together, these findings support the relevance of systemic inflammatory markers in characterizing disease features in breast cancer. In the future, studies with larger sample size are required to clarify their clinical significance.

Conflicts of Interest: The authors declare no conflicts of interest.

Institutional Review Board Statement: This study was approved by the Hue University of Medicine and Pharmacy, Hue University Ethics Committee in 2025, approval number H2025/426.

Funding: This study was funded by Hue University, grant number DHH2025-04-233.

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