

Age-Dependent Differences in Inflammatory Blood Markers Associated with Breast Cancer Recurrence after Surgery

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Abstract

Background

Systemic inflammatory markers may predict prognosis after curative breast cancer surgery. This study evaluated the prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for postoperative recurrence according to age.

Methods

In this retrospective cohort study, 200 women who underwent curative breast cancer surgery between 2022 and 2024 were followed for a mean of 24.3 ± 1.5 months. Clinical, pathological, and inflammatory parameters were extracted from medical records. Outcomes included disease recurrence and all-cause mortality.

Results

Disease recurrence occurred in 10 patients (4.5%), with a higher incidence in patients > 65 years than in those ≤ 65 years (11.4% vs. 2.8%, $p = 0.015$). Mortality was low (1.4%) and did not differ between age groups ($p = 0.561$). Among patients ≤ 65 years, those with recurrence had significantly higher preoperative NLR than those without recurrence (5.39 ± 3.30 vs. 2.36 ± 1.31 , $p = 0.001$). In patients > 65 years, recurrence was associated with significantly lower PLR (109.37 ± 17.42 vs. 143.65 ± 51.39 , $p = 0.042$). The optimal NLR cutoff for predicting recurrence in younger patients was 2.4 (75.0% sensitivity, 65.6% specificity), whereas the optimal PLR cutoff in older patients was 97 (78.4% sensitivity, 62.7% specificity).

Conclusion

Age influences the prognostic significance of preoperative inflammatory markers in breast cancer. Elevated NLR in patients ≤ 65 years and reduced PLR in those > 65 years were associated with an increased risk of postoperative recurrence and may serve as simple, readily available prognostic biomarkers.

INTRODUCTION

After lung cancer, breast cancer is the second most common cause of cancer-related deaths in women [1]. As life expectancy rises, we are dealing with a global demographic shift known as the "silver tsunami," which is a growing percentage of the population that is older. Women between the ages of 70 and 79 have the highest risk of being diagnosed with breast cancer, and this risk rises with age [1]. Currently, women 70 years of age or older account for one-third of all cases of breast cancer [2]. The

percentage of older women who receive a breast cancer diagnosis will rise in tandem with the population's aging, and it is predicted that during the next three decades, the number of new cases among women aged 70 and older will more than double globally [3]. Despite making up a sizable share of breast cancer patients, the elderly are underrepresented in clinical trials and the best ways to treat them are not well established [4, 5]. There are currently few standardized guidelines addressing recommended treatments for women over 70 years of age, and there are few studies looking at the results of breast surgery for these women [2, 6]. The underutilization of reconstruction and oncoplastic breast-conserving surgery (BCS) in the elderly is reflected in the paucity of evidence in the literature [2, 7, 8].

Growing older is a significant risk factor for the development of breast cancer. Additionally, it has been suggested that breast cancer survival is impacted by the patient's age at diagnosis. A distinct clinical-pathological pattern of features, variations in treatment patterns (specifically, de-escalation approaches), and worse outcomes have all been linked to older age at diagnosis [1–3]. In contrast, research has shown that despite the subtype and intensive treatment typically used, a young age at breast cancer diagnosis is linked to a distinct set of clinical-pathological characteristics and may independently have a detrimental effect on survival [8, 9]. Regardless of the stage at which they first present, a number of recent studies have indicated that young women have worse outcomes [10–12]. Unfavorable pathological characteristics or biomarker status are partially blamed by some for these inconsistent results [13, 14]. However, when limited to cancers that are node negative or in an earlier stage, other studies only indicate worse outcomes for young women [15, 16].

In addition to pointing out that peripheral blood inflammatory markers have some use in cancer treatment and prognosis prediction, prior research has demonstrated that the systemic inflammatory response plays a significant role in the occurrence and development of tumors [5, 6]. Systemic inflammation is indicated by the blood neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), hemoglobin and albumin levels, and lymphocyte and platelet counts (HALP). Tumor incidence, progression, and outcome have previously been associated with indicators of systemic inflammation [17, 18]. However, the association between systemic inflammatory markers and the prognosis and treatment effectiveness in patients with breast cancer remains controversial [19, 20], and there are few reports on the association between those markers and the prognosis and treatment effectiveness in patients with breast cancer. Importantly, given the apparent difference in surgical prognosis of breast cancer in younger and older patients, it is unclear whether the diagnostic and prognostic value of these inflammatory markers is similar in the two age groups. Therefore, we investigated the association between the prognosis of breast cancer surgery and the preoperative systemic inflammatory indicators (NLR and PLR).

MATERIALS AND METHODS

Study population

The current retrospective cohort study was performed on all consecutive women underwent curative breast cancer surgery at Okan University Hospital in Istanbul, Turkey between 2022 and 2024. The eligibility to including the subjects was to histologically confirm invasive breast cancer leading mastectomy as well as with available of study baseline parameters and studied laboratory indices in the hospital recorded files. Those with active infections, autoimmune diseases, or hematologic disorders were excluded to minimize confounding effects on inflammatory indices. Patients were stratified according to age (< 65 years and ≥ 65 years). The cutoff of 65 years was selected because it is a widely accepted threshold for defining older adults in oncology and geriatric research and has been frequently used in breast cancer studies evaluating age-related differences in clinical outcomes and systemic inflammatory responses [21–23]. Furthermore, age-related changes in immune and inflammatory function become more pronounced after this age, making it a clinically relevant threshold for the present analysis. A small number of patients classified as TNM stage IV were included because they underwent surgery with curative intent in the context of oligometastatic disease or isolated resectable metastasis following multidisciplinary team decision-making (after favorable response to systemic therapy and absence of widespread progression). In these selected cases, surgery was performed as part of an aggressive multimodal treatment strategy aiming at potential long-term disease control rather than purely palliative intent

Data collection

Clinical and pathological variables (including age, tumor histological grade, TNM grade, laboratory parameters and adjuvant treatments) were extracted from patients' medical records. In this study, NLR was defined as absolute neutrophil count divided to absolute lymphocyte count and PLR as absolute platelet count divided to absolute lymphocyte count.

Study outcome

Follow-up data were also collected from institutional cancer registries and outpatient records. The following outcome was disease recurrence defined as the reappearance of malignant breast epithelial cells after a clinically and pathologically confirmed period of complete remission following primary therapy within the follow-up period. In our study, the patients were followed-up for a mean time of 24.75 ± 18.34 months ranged 4 months and 6 years.

Statistical analysis

Prior to statistical analyses, the distributional assumptions of continuous variables were assessed using both graphical methods (histograms and Q–Q plots) and the Shapiro–Wilk test for normality. Homogeneity of variances between groups was evaluated using Levene's test. All continuous variables demonstrated approximately normal distributions and satisfied variance homogeneity assumptions. Therefore, continuous variables were summarized as mean $\pm$ standard deviation (SD) and compared between groups using Student's t-test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. The

distributions of NLR and PLR were specifically evaluated because these biomarkers are often reported as non-normally distributed variables. Assessment by histograms, Q–Q plots, and the Shapiro–Wilk test demonstrated approximate normality without substantial skewness; therefore, these variables were summarized as mean $\pm$ standard deviation and analyzed using parametric statistical methods. Survival curves were plotted using the Kaplan–Meier method and compared by the log-rank test. Multivariable Cox proportional hazards regression analysis was performed to identify independent predictors of disease recurrence. Covariates were selected based on clinical relevance and univariate analysis results. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Given the limited number of recurrence events, the multivariable model should be considered exploratory, and results should be interpreted with caution due to the potential risk of overfitting. No penalized regression methods or internal validation procedures were applied. Receiver operating characteristic (ROC) curve analysis was performed using nonparametric methods based on empirical distributions of NLR and PLR values. Sensitivity and specificity were calculated across all observed thresholds of the continuous variables. The optimal cut-off values were determined using the Youden index. Given the limited number of recurrence events, ROC curves may exhibit stepwise characteristics, and performance estimates should be interpreted with caution. All analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). All statistical tests were performed as two-sided tests, and a two-sided P value < 0.05 was considered statistically significant.

RESULTS

Overall, 200 women with the definitive diagnosis of breast cancer underwent curative breast cancer surgery were included into the study. The average age of the participants was 54.11 ± 13.55 years ranged 30 to 90 years. In this regard, 176 aged equal to or younger than 65 years and 44 aged higher than 65 years. Table 1 summarized the baseline characteristics and pathological parameters in these two age subgroups. The prevalence rate of traditional risk factors (hyperlipidemia, hypertension, chronic cardiovascular disorders, history of stain use, and also Ki-67 state were significant different between the two age subgroups. As shown in Table 2, the younger adults had significantly lower tumor grade as well as lower mean white blood cell (WBC) count as compared to older participant. However, there was no difference in the values of NLR and PLR between the two age subgroups.

Table 1
Baseline clinical and pathophysiological characteristics

Characteristics	Total (n = 200)	Age ≤ 65 years (n = 176)	Age > 65 years (n = 44)	P-value
Mean age, year	54.11 ± 13.55	49.10 ± 9.71	74.18 ± 6.09	< 0.001
Clinical stage (TNM), %				0.157
1	80 (36.4)	60 (34.1)	20 (45.5)	
2A	76 (34.5)	60 (34.1)	16 (36.4)	
2B	40 (18.2)	37 (21.0)	3 (6.6)	
3A	11 (5.0)	9 (5.1)	2 (4.5)	
3B	1 (0.5)	1 (0.6)	0 (0.0)	
3C	5 (2.3)	2 (1.1)	3 (6.8)	
4	7 (3.2)	7 (4.0)	0 (0.0)	
Pathological TNM stage (TNM), %				0.097
1	101 (45.9)	87 (49.4)	14 (31.8)	
2A	62 (28.2)	44 (25.0)	18 (40.9)	
2B	25 (11.4)	22 (12.5)	3 (6.8)	
3A	21 (9.5)	14 (8.0)	7 (15.9)	
3B	0 (0.0)	0 (0.0)	0 (0.0)	
3C	7 (3.2)	2 (2.8)	2 (4.5)	
4	4 (1.8)	4 (2.3)	0 (0.0)	
Tumor grade, %				0.005
I	46 (20.9)	44 (25.0)	2 (4.5)	
II	105 (47.7)	83 (47.2)	22 (50.0)	
III	69 (31.4)	49 (27.8)	20 (45.5)	
Neoadjuvant therapy, %	72 (32.7)	63 (35.8)	9 (20.5)	0.072
Current/former smoking	52 (23.6%)	38 (21.6%)	14 (31.8%)	0.126
Diabetes mellitus	42 (19.1%)	27 (15.3%)	15 (34.1%)	0.092
Hyperlipidemia	61 (27.7%)	42 (23.9%)	19 (43.2%)	0.018
Hypertension	74 (33.6%)	44 (25.0%)	30 (68.2%)	0.001

Characteristics	Total (n = 200)	Age ≤ 65 years (n = 176)	Age > 65 years (n = 44)	P-value
Chronic cardiovascular disease	28 (12.7%)	14 (8.0%)	14 (31.8%)	0.001
NSAID use	36 (16.4%)	25 (14.2%)	11 (25.0%)	0.129
Statin use	49 (22.3%)	31 (17.6%)	18 (40.9%)	0.002
ER positive	165 (75.0%)	128 (72.7%)	37 (84.1%)	0.456
PR positive	145 (65.9%)	118 (67.0%)	27 (61.4%)	0.772
HER2 positive	44 (20.0%)	38 (21.6%)	6 (13.6%)	0.129
Ki-67 < 20%	112 (50.9%)	82 (46.6%)	30 (68.2%)	0.027
Ki-67 ≥ 20%	108 (49.1%)	94 (53.4%)	14 (31.8%)	0.002
Luminal A	92 (41.8%)	68 (38.6%)	24 (54.5%)	0.001
Luminal B HER2-	66 (30.0%)	56 (31.8%)	10 (22.7%)	0.456
Luminal B HER2+	22 (10.0%)	18 (10.2%)	4 (9.1%)	0.728
HER2-enriched	18 (8.2%)	16 (9.1%)	2 (4.5%)	0.226
Triple-negative	22 (10.0%)	18 (10.2%)	4 (9.1%)	0.779

Table 2
The data of inflammatory indices

Characteristics	Total (n = 200)	Age ≤ 65 years (n = 176)	Age > 65 years (n = 44)	P-value
Laboratory parameters				
Mean WBC count, ×10 ⁹ /L	6.53 ± 1.83	6.32 ± 1.83	7.14 ± 1.74	0.024
Mean neutrophil count, ×10 ⁹ /L	4.03 ± 1.65	3.95 ± 1.72	4.35 ± 1.31	0.170
Mean lymphocyte count, ×10 ⁹ /L	1.86 ± 0.66	1.83 ± 0.69	1.98 ± 0.51	0.209
Mean platelet count, ×10 ⁹ /L	256.57 ± 66.48	255.05 ± 68.50	262.67 ± 58.08	0.513
Mean NLR ratio	3.07 ± 0.76	3.87 ± 0.85	2.27 ± 0.65	0.197
Mean PLR ratio	159.59 ± 102.86	164.28 ± 111.96	141.08 ± 50.37	0.203

The mean follow-up time in the group ≤ 65 years and in older ones was 22.81 ± 17.35 months and 26.70 ± 19.39 respectively with no difference (p = 0.556). Regarding study outcome in the following-up, disease

recurrence following surgery was revealed in 10 patients (4.5%) as 2.8% in patients younger than 65 years and 11.4% in those who were older indicating a significant difference ($p = 0.015$). Postoperative death during follow-up time also occurred in 1.4% (1.1% in patients aged ≤ 65 years and 2.3% in patients aged > 65 years) indicating no difference ($p = 0.561$). The 1, 2, and 3 years disease recurrence-free survival in patients younger than 65 years was 98.8%, 97.0%, and 97.0% and in older ones was 95.0%, 95.0%, and 87.7% respectively (Fig. 1).

Comparing the groups with and without recurrence regarding laboratory parameters showed significantly higher mean WBC count (8.15 ± 0.79 versus 6.48 ± 1.83 , $p = 0.017$), higher mean NLR (4.05 ± 1.88 versus 2.35 ± 1.22 , $p = 0.003$), as well as lower PLR (116.54 ± 27.91 versus 155.14 ± 65.23 , $p = 0.009$) in the former group (Table 3). In the subgroup of patients younger than 65 years, we found significantly higher mean NLR in those who experienced recurrence (5.39 ± 3.30 versus 2.36 ± 1.31 , $p = 0.001$), but without any difference in mean PLR between the groups with and without disease recurrence (Table 3). In patients older than 65 years old, there was no difference in the mean NLR between the subgroups with and without disease recurrence, however those who had disease recurrence had significantly lower rate of PLR than in those without experience of recurrence (109.37 ± 17.42 versus 143.65 ± 51.39 , $p = 0.042$) (Table 3). Using the Cox proportional hazard modeling (Table 4), higher NLR (HR = 2.779, $P = 0.034$) and lower PLR (HR = 0.689, $P = 0.008$) could effectively predict disease recurrence in breast cancer patients adjusting baseline parameters.

Table 3

The value of laboratory parameters in the groups with and without recurrence

Characteristics	Recurrence (+) (n = 10)	Recurrence (-) (n = 210)	P-value
Total			
Mean WBC count, /mm ³	8.15 ± 0.79	6.48 ± 1.83	0.017
Mean neutrophil count, /mm ³	5.16 ± 2.19	3.99 ± 1.61	0.210
Mean lymphocyte count, /mm ³	1.82 ± 0.80	1.86 ± 0.66	0.893
Mean platelet count, /mm ³	218.52 ± 74.23	258.12 ± 65.89	0.179
Mean NLR ratio	4.05 ± 1.88	2.35 ± 1.22	0.003
Mean PLR ratio	116.54 ± 27.91	155.14 ± 65.23	0.009
Age ≤ 65 years			
Mean WBC count, /mm ³	7.54 ± 0.54	6.30 ± 1.84	0.345
Mean neutrophil count, /mm ³	5.42 ± 2.75	3.92 ± 1.68	0.084
Mean lymphocyte count, /mm ³	1.55 ± 1.00	1.84 ± 0.69	0.422
Mean platelet count, /mm ³	205.54 ± 87.06	256.61 ± 67.59	0.101
Mean NLR ratio	5.39 ± 3.30	2.36 ± 1.31	0.001
Mean PLR ratio	121.91 ± 35.58	157.90 ± 67.99	0.133
Age > 65 years			
Mean WBC count, /mm ³	8.76 ± 0.36	7.04 ± 1.74	0.006
Mean neutrophil count, /mm ³	4.82 ± 1.66	4.32 ± 1.29	0.525
Mean lymphocyte count, /mm ³	2.18 ± 1.53	1.96 ± 0.52	0.498
Mean platelet count, /mm ³	240.16 ± 54.78	264.45 ± 58.65	0.493
Mean NLR ratio	2.25 ± 0.90	2.30 ± 0.78	0.919
Mean PLR ratio	109.37 ± 17.42	143.65 ± 51.39	0.042

Table 4
Cox proportional hazard analysis for determining the value of NLR and PLR for predicting disease recurrence

Item	Beta	SE	P-value	HR	95% CI for HR	
					Lower	Upper
WBC	0.002	0.012	0.889	1.002	0.999	1.008
NLR	0.526	0.412	0.034	2.779	1.624	8.126
PLR	0.036	0.034	0.008	0.689	0.221	0.812
Age65	0.264	1.312	0.779	1.312	0.092	6.715
grade	2.121	1.471	0.178	6.129	0.442	9.675
TNM	0.234	0.479	0.445	1.278	0.326	3.758
Smoking	0.122	0.097	0.079	1.112	0.789	1.478
Diabetes mellitus	2.112	1.456	0.008	2.126	1.074	5.246
Hyperlipidemia	0.456	0.478	0.226	1.246	0.786	1.349
Hypertension	0.222	0.212	0.565	1.012	0.753	1.402
Cardiovascular disease	0.126	0.246	0.234	1.145	0.779	2.240
NSAID use	0.112	0.126	0.785	0.428	0.212	1.479
Statin use	0.782	0.646	0.246	1.105	0.982	1.226
ER positive	0.478	0.456	0.723	0.478	0.270	1.145
PR positive	0.378	0.278	0.345	0.299	0.089	1.789
HER2 positive	0.782	0.612	0.244	0.678	0.247	1.478
Ki-67 status	0.478	0.245	0.127	1.123	0.412	1.786
pathological subtype	1.147	0.324	0.036	1.456	1.102	3.478

According to the ROC curve analysis, in patients younger than 65 years, assessing NLR could effectively discriminate recurrence from non-recurrence states (AUC = 0.715). The best cutoff value of NLR to predict recurrence was 2.4 yielding a sensitivity of 75.0% and a specificity of 65.6% (Fig. 2). In similar analysis, in those who older than 65 years, lower PLR could differentiate recurrence from non-recurrence conditions (AUC = 0.730). The bet cutoff point for PLR to predict disease recurrence was 97 with a sensitivity of 78.4% and specificity of 62.7% (Fig. 3). Due to low death rate in our study population, performing similar analyses to predict death was not possible.

DISCUSSION

This study investigated the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in predicting long-term disease recurrence among women with breast cancer undergoing curative surgery. The findings highlight a nuanced relationship between systemic inflammatory markers and recurrence risk, particularly in the context of patient age. Specifically, higher NLR values were associated with increased recurrence risk in patients younger than 65 years, whereas lower PLR values were predictive of recurrence in patients aged 65 years and older. The results emphasize the complexity of host immune and inflammatory responses in modulating tumor biology after curative resection. Elevated PLR in younger patients may reflect a pro-tumorigenic inflammatory microenvironment, characterized by increased platelet activity and relative lymphopenia [24]. Platelets can promote tumor growth and metastasis through multiple mechanisms, including the release of vascular endothelial growth factor (VEGF), shielding tumor cells from immune surveillance, and facilitating epithelial-mesenchymal transition [25]. Hence, a higher PLR might mirror systemic inflammation and impaired antitumor immunity, explaining its correlation with recurrence in this subgroup. Some similar evidences are available emphasizing the close association of NLR with poorer outcome of breast cancer. As indicated by Truffi et al in 2021 [26], preoperative lymphocyte ratios, in particular PLR and NLR showed prognostic relevance in ER+ HER2- early breast cancer. In another survey by Grassadonia et al in 2021 [27], low NLR remained independent prognostic factor for disease-free survival, while only post-treatment low NLR affected overall survival in women suffering Luminal Breast Cancer. Moreover, Orditura et al [28] also indicated that low NLR value (HR = 2.52) was an independent prognostic variable of distant metastasis-free survival.

Conversely, the observation that lower PLR values were linked to recurrence in the older population suggests that immunosenescence and age-related hematologic changes may alter the biological interpretation of inflammatory indices. In elderly patients, baseline platelet counts tend to decline and lymphocyte function is often diminished due to decreased thymic output and chronic low-grade inflammation (“inflammaging”) [29]. Thus, a lower PLR in older individuals may paradoxically correspond to weakened immune competence rather than a favorable immunologic state, making tumor recurrence more likely. This bidirectional effect underscores the necessity of age-specific thresholds when interpreting inflammatory biomarkers. In some studies, the value of PLR in predicting poorer outcome has been also tested. Guo et al [30] could revealed that PLR was associated with overall survival as well as high risk of recurrence for breast cancer patients especially in HER2-positive patients. Also, Hu et al in 2020 [31] showed that the pretreatment PLR is superior to the NLR as a predictor of pathologic complete response and disease-free survival outcomes in patients with luminal B-like (HER2-) breast cancer.

Interestingly, the study’s incorporation of both NLR and PLR maintains theoretical relevance. While NLR has been widely validated as a marker of systemic inflammation and poor cancer outcomes, PLR may capture distinct biological dimensions related to platelet-driven tumorigenesis. The differential impact of PLR across age groups suggests that it might be more sensitive to host-related factors than NLR, especially in the context of postoperative immune modulation.

Despite obtaining significant evidence regarding the prognostic role of the two inflammatory markers of NLR and PLR, some studies also failed to obtain such evidence. As shown in a recent study by Bulut et al [32] progression-free survival was not significantly associated with both NLR and PLR. Similarly, in Nong et al study in 2026 [33], subgroup analysis revealed that although high serum amyloid A was independently correlated with both worse event-free survival and overall survival, the independent associations of NLR and PLR with clinical outcomes were lost after adjusting for clinical confounders. Several factors may contribute to these inconsistencies. First, breast cancer is a biologically heterogeneous disease, and the association between systemic inflammatory markers and survival may differ according to molecular subtype, hormone receptor status, HER2 expression, and tumor grade. Second, variations in patient populations, including age distribution, comorbidity burden, ethnic background, and baseline inflammatory conditions, may influence NLR and PLR values independently of tumor biology. Third, differences in treatment strategies, such as the use of neoadjuvant chemotherapy, adjuvant systemic therapy, radiotherapy, and targeted treatments, can modify survival outcomes and potentially confound the prognostic significance of inflammatory biomarkers. Moreover, studies have employed different cutoff values for NLR and PLR, derived from receiver operating characteristic analyses, median values, or previously published thresholds, limiting comparability across cohorts. Methodological differences, including retrospective versus prospective designs, sample size, duration of follow-up, and adjustment for confounding variables, may further contribute to divergent findings. Finally, perioperative factors and transient inflammatory responses related to surgery or concurrent infections may affect biomarker measurements and introduce additional variability. These sources of heterogeneity should be considered when interpreting the prognostic role of NLR and PLR in patients undergoing breast cancer surgery.

Although our findings support the prognostic significance of NLR and PLR in patients undergoing breast cancer surgery, these biomarkers should be considered complementary rather than alternative tools to established prognostic models. Current risk stratification in breast cancer relies primarily on clinicopathological factors, including tumor size, nodal status, histological grade, lymphovascular invasion, hormone receptor expression, HER2 status, and proliferation markers such as Ki-67, as well as molecular and genomic assays including Oncotype DX and related multigene signatures. These approaches primarily characterize the intrinsic biological behavior of the tumor, whereas NLR and PLR reflect the host systemic inflammatory and immune response to cancer. Consequently, inflammatory biomarkers may provide additional prognostic information that is not captured by conventional tumor-centered parameters. The integration of NLR and PLR into existing prognostic frameworks could potentially improve risk discrimination by incorporating both tumor biology and host-related factors. In particular, these inexpensive and readily available biomarkers may be useful in settings where access to genomic testing is limited or as adjunctive markers for refining prognostic estimates within clinically or molecularly defined risk groups. Future prospective studies should evaluate whether the addition of NLR and PLR to established clinicopathological and molecular models results in meaningful improvements in prognostic accuracy and clinical decision-making.

An important consideration when interpreting our findings is the presence of baseline clinicopathological differences between the age groups. Tumor grade was significantly different between younger and older patients, and some imbalance in stage distribution was also observed. Because both tumor grade and disease stage are strong determinants of breast cancer recurrence and survival, these differences may have partially influenced the observed associations between inflammatory biomarkers and clinical outcomes. It is therefore possible that age-related variations in tumor biology, in addition to age-related changes in host inflammatory and immune responses, contributed to the differential prognostic performance of PLR observed in this study. Although our analyses focused on the prognostic value of inflammatory markers, residual confounding from established tumor-related prognostic factors cannot be excluded. Consequently, the results should be interpreted with caution and viewed as hypothesis-generating until validated in larger prospective cohorts with comprehensive adjustment for molecular subtype, tumor grade, stage, and other clinicopathological characteristics.

These findings contribute to the growing body of evidence supporting the integration of hematologic ratios into prognostic modeling in breast cancer. However, variability in cutoff definitions, timing of measurement (preoperative vs. postoperative), tumor subtype distributions, and comorbidity profiles may limit direct comparison with earlier studies [24–27]. Moreover, the retrospective nature of most analyses, including the current one, precludes definitive causal inference. Future prospective studies should aim to validate age-specific PLR and NLR cutoffs, explore their dynamic changes during the perioperative period, and integrate these markers into multivariate models alongside well-established prognostic factors such as tumor stage, receptor status, and Ki-67 index. An important limitation of the ROC analysis is the small number of recurrence events, which inherently restricts the resolution and stability of sensitivity and specificity estimates. This results in stepwise ROC curves with relatively coarse increments in performance measures. Accordingly, reported accuracy metrics should be interpreted cautiously, and validation in larger cohorts with higher event numbers is required to obtain more stable and generalizable estimates. A key limitation of the present study is the small number of recurrence events, which restricts the robustness of multivariable Cox regression analysis. Despite limiting the number of covariates, the events-per-variable ratio remains low, increasing the risk of model overfitting and instability of hazard ratio estimates. Additionally, penalized regression techniques or internal validation methods were not employed. Therefore, the reported associations should be considered exploratory and require confirmation in larger, adequately powered studies. As another potential limitation, multivariable regression analyses with a low number of outcome events may increase the risk of overfitting and yield unstable estimates. In fact, the limited number of events may affect the robustness of hazard ratio estimates and that the findings should therefore be interpreted with caution. In final, the relatively small sample size of the older age subgroup ($n = 44$) results in an imbalance between comparison groups, which may limit the statistical power and precision of subgroup analyses. This imbalance could potentially affect the stability and generalizability of the subgroup findings. It should be also noted that the study population originates from a single center in Turkey without discussion of ethnic or regional generalizability. Also, an additional limitation relates to the determination of NLR and PLR cut-off values. The optimal thresholds were derived post hoc from the

same dataset in which their prognostic performance was subsequently evaluated. As a result, these cut-offs are exploratory and subject to potential overfitting and optimism bias. This limitation is particularly important given the relatively small number of recurrence events, which may reduce the stability of threshold estimation and increase the likelihood of chance findings. Consequently, the identified NLR and PLR cut-off values should be regarded as hypothesis-generating rather than definitive clinical thresholds. Independent validation in larger, external cohorts is necessary to determine whether these age-specific cut-offs are reproducible and clinically meaningful.

CONCLUSION

The present study suggests that the prognostic significance of both systemic inflammatory markers of NLR and PLR, may be age-dependent in women with breast cancer undergoing curative surgery. A higher NLR was associated with an increased risk of long-term disease recurrence in patients younger than 65 years, whereas a lower PLR appeared to be associated with poorer outcomes in those aged 65 years and older. These findings highlight the potential influence of age-related hematologic and immunologic variability on the prognostic performance of inflammatory biomarkers. However, given the retrospective design and the inherent limitations of observational analyses, these results should be considered preliminary and hypothesis-generating. While NLR and PLR may have potential value as adjunctive prognostic markers, their clinical utility and incremental benefit beyond established prognostic factors remain to be determined. Prospective validation in large, multi-center cohorts and further investigation of the underlying biological mechanisms is required before these biomarkers can be considered for routine incorporation into clinical decision-making or post-surgical surveillance strategies.

Declarations

The authors have no conflict of interest (none declare)

Ethics Committee Approval

The approval of this study in accordance with the ethical rules of the Declaration of Helsinki was approved by the ethics committee of Istanbul Okan University at the meeting numbered 191 on 30.05.2025. The written informed consent to participate was obtained from all of the participants in the study.

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Consent for publication

Not Applicable

Conflict of Interest

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Author Contribution

KG: Conceptualization, Methodology, Investigation, Supervision, Writing – Original DraftDD: Data Curation, Investigation; MS: Formal Analysis, Validation, Data Interpretation, Writing – Review & Editing. All authors reviewed the manuscript, approved the final version for publication, and agreed to be accountable for all aspects of the work.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

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Figures

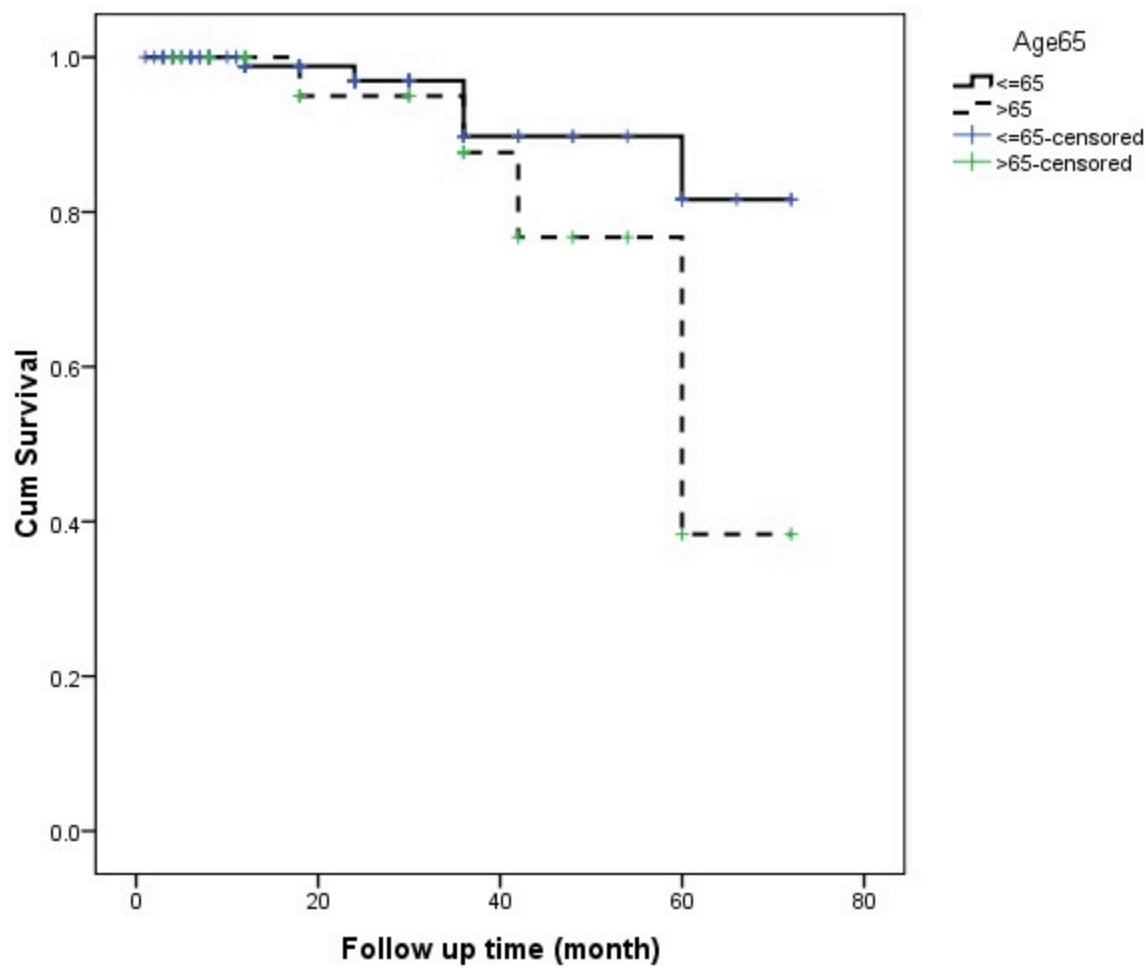


Figure 1

The Kaplan-Meier survival analysis to determine the recurrence-free survival according to patients' age

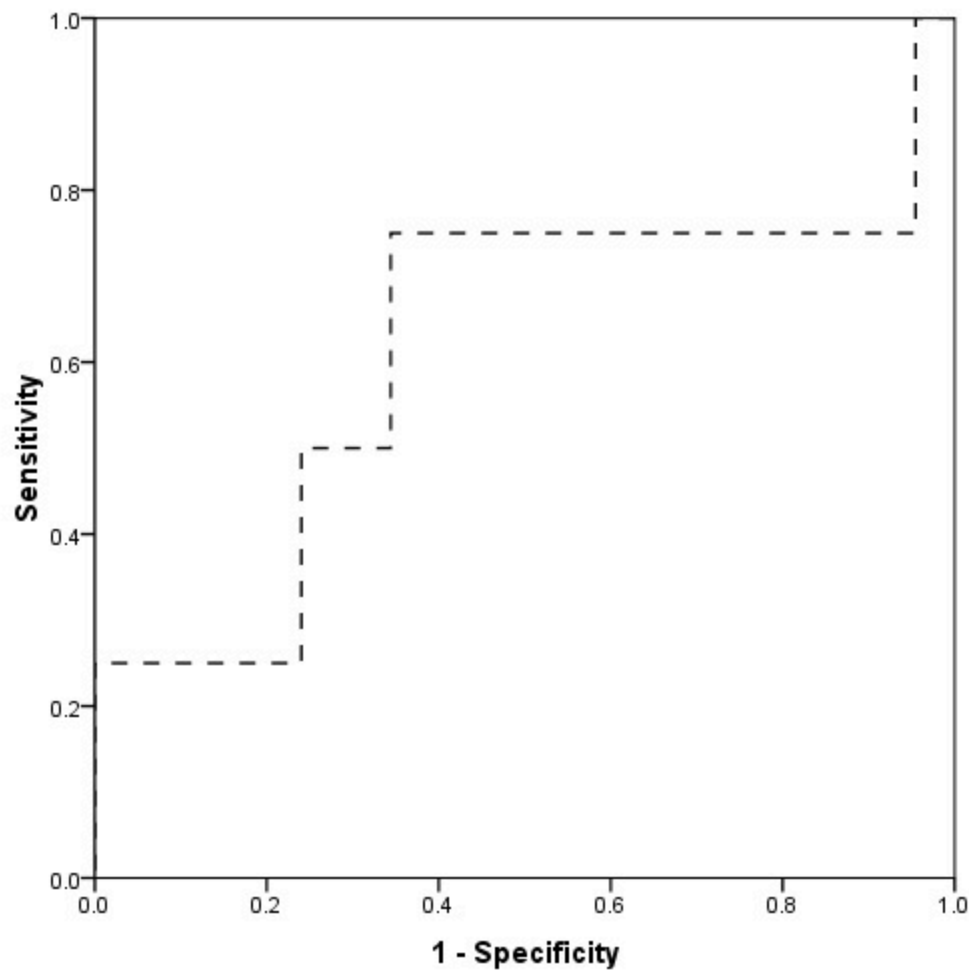


Figure 2

The ROC curve analysis with the aim to determine the value of NLR to predict disease recurrence in patients younger than 65 years

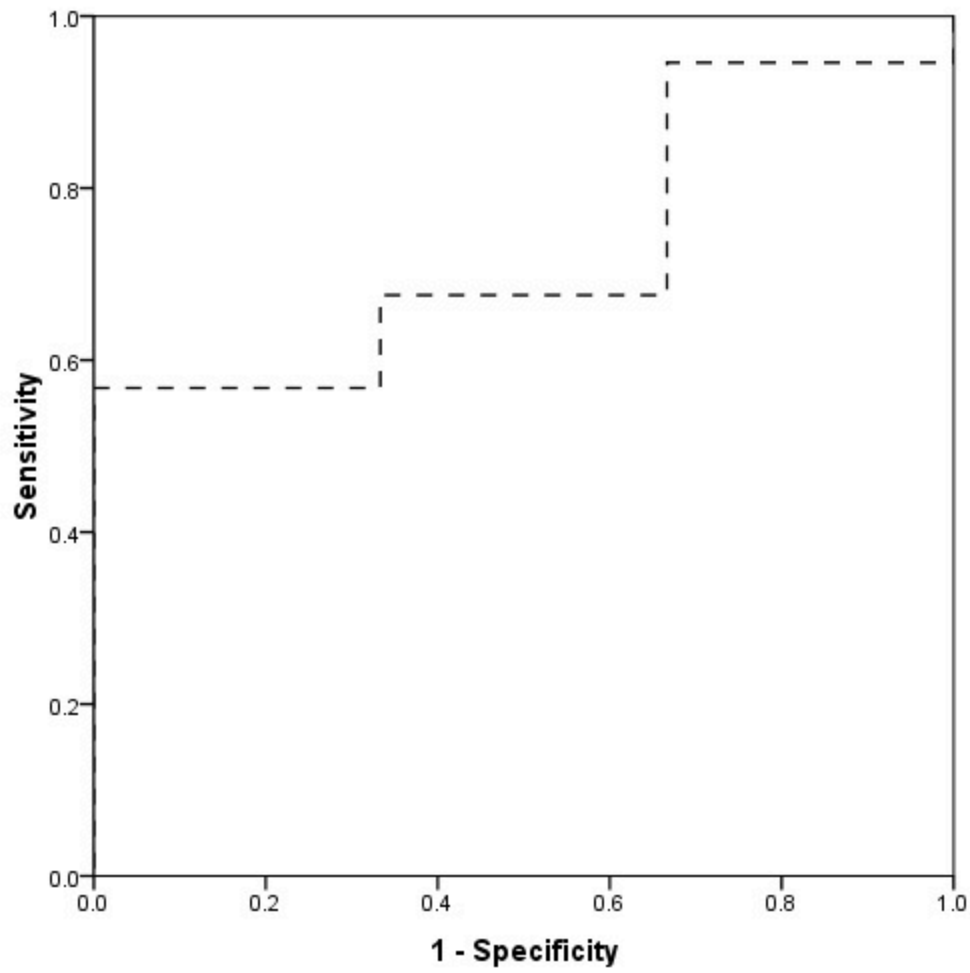


Figure 3

The ROC curve analysis with the aim to determine the value of PLR to predict disease recurrence in patients older than 65 years