

Research Article

Do Inflammatory Indices Have Prognostic Value in Metastatic Breast Cancer Patients Receiving CDK 4/6 Inhibitor Therapy?

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Abstract

Objectives: This study aims to elucidate the prognostic significance of biomarkers indicative of inflammation, including the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio (CAR), and hemoglobin, albumin, lymphocyte, and platelet (HALP) scores, prior to treatment with CDK4/6 inhibitors in patients with hormone receptor-positive (HoR+)/HER2-negative (HER2-) advanced breast cancer.

Methods: The study cohort comprised patients monitored at Balıkesir Atatürk City Hospital, those with HoR+/HER2-metastatic breast cancer undergoing first-line CDK4/6 inhibitor therapy. PLR is defined as the platelet-to-lymphocyte ratio, NLR as the ratio of neutrophil count to lymphocyte count, CAR as the C-reactive protein-to-albumin ratio, and the HALP score is calculated as $[\text{hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocytes (/L)}] / \text{platelets (/L)}$. Receiver operating characteristic (ROC) curve analysis was employed to determine the optimal cut-off values for these markers and to perform sensitivity-specificity calculations. Cox regression analysis was utilized for univariate survival risk analysis, and the Forward Stepwise (Likelihood Ratio) method was applied to the multivariate models.

Results: A total of 38 patients with HR+/HER2- metastatic breast cancer were included. The median age was 59.5 years, and 78.9% were postmenopausal. Disease progression occurred in 55.2% of patients, and 7.8% died during follow-up. ROC analysis identified optimal prognostic cut-off values for PLR (128; AUC = 0.786, $p=0.003$) and HALP (32.6; AUC = 0.875, $p=0.001$), while NLR and CAR were not significant predictors. Median overall survival (OS) was 45 months, which was shorter in pre/perimenopausal patients and those with visceral metastases or elevated CAR (≥ 0.75). Multivariate analysis confirmed menopausal status, visceral metastasis, and high CAR as independent prognostic factors for OS.

Conclusion: The CAR index is a reliable, straightforward, readily accessible, and cost-efficient tool for predicting the prognosis of patients with metastasis.

Keywords: Breast cancer, cdk 4/6 inhibitor, inflammatory indices

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Breast cancer represents the most prevalent malignancy and the second most common cause of cancer-associated mortality among women worldwide.^[1–3] This clinically heterogeneous disease is molecularly classified based on the expression status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which collectively define four principal subtypes with

distinct biological behaviors and therapeutic implications: (I) hormone receptor-positive/HER2-negative (HR+/HER2-), (II) hormone receptor-positive/HER2-positive (HR+/HER2+), (III) hormone receptor-negative/HER2-positive (HR-/HER2+), and (IV) triple-negative breast cancer (TNBC).^[4]

HR+ and HR- breast cancers exhibit distinct clinical behaviors.^[5] HR+ luminal cancers are further classified into luminal

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A (characterized by low expression of proliferation-related genes and high expression of ER-related genes) and luminal B (characterized by high expression of proliferation-related genes and low expression of ER-related genes).^[5]

Breast cancer treatment is determined by its molecular subtype, a principle applicable to both early-stage and advanced-stage disease.^[6] Among these, luminal-subtype tumors demonstrate the most favorable prognosis, with patients benefiting from endocrine therapy.^[7] Over the past decade, CDK4/6 inhibitors have become the standard treatment for metastatic HR+/HER2– breast cancer.^[8] The three available CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—have been extensively studied in combination with endocrine therapy (ET) for metastatic breast cancer (mBC), demonstrating improved progression-free survival (PFS). Notably, ribociclib has emerged as the preferred first-line agent for mBC due to its overall survival (OS) advantage over endocrine monotherapy.^[8]

However, ET resistance in mBC remains a significant therapeutic challenge, necessitating the identification of novel biomarkers to better understand and overcome this resistance.^[7] Although molecular-based predictive biomarkers have been developed, their accessibility remains limited in developing countries.^[9]

Recent research highlights the role of systemic inflammation in tumor development and progression.^[10–12] Inflammatory indices, such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP)/albumin ratio (CAR), and HALP score, are derived from routine blood parameters and have been used to predict prognosis in various cancers.^[13–15] Both the HALP score and CAR also reflect inflammation and nutritional status in cancer patients.^[10, 11] In breast cancer, elevated PLR, NLR, and CAR values, along with reduced HALP scores, serve as negative prognostic indicators and correlate with poor treatment response.^[13–23]

This study aimed to evaluate the prognostic value of pre-treatment peripheral blood biomarkers (PLR, NLR, CAR, HALP score) and clinicopathological characteristics in patients with HR+/HER2– advanced breast cancer receiving CDK4/6 inhibitor therapy.

Methods

The study included female patients with estrogen receptor (ER) levels $\geq 10\%$, diagnosed with metastatic invasive ductal carcinoma (IDC) at initial presentation, and who had not received prior chemotherapy or anti-hormone therapy. Participants were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2. The cohort comprised patients diagnosed between January 1, 2021,

and January 1, 2025, treated at the Medical Oncology Clinic of Balıkesir Atatürk City Hospital. Due to reimbursement policies for CDK4/6 inhibitors in our country, eligible patients had ER levels $\geq 10\%$ and received either palbociclib or ribociclib. However, patients receiving abemaciclib were not included in the study due to the lack of insurance coverage for this medication, as per institutional prescribing guidelines. The treatment regimen included aromatase inhibitor therapy (standard first-line treatment), and patients with bone metastasis received denosumab or bisphosphonates.

Exclusion criteria were male breast cancer, prior systemic therapy, ER levels $< 10\%$, ECOG PS ≥ 3 , active infection, organ dysfunction, anti-inflammatory drug use, and significant comorbidities that might affect study outcomes.

The Ki67 immunohistochemistry (IHC) proliferation marker cutoff was set at 30%.^[24] ER and PR analyses followed American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.^[25] PLR was defined as the platelet-to-lymphocyte ratio, NLR as the neutrophil-to-lymphocyte ratio, CAR as the CRP-to-albumin ratio, and the HALP score was calculated as $[\text{hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocytes (/L)}] / \text{platelets (/L)}$.^[26] Pretreatment laboratory values (within one week before therapy initiation) were used. Additionally, OS was defined as the time from randomization to death.

Statistical Analysis

Data are presented as numbers, percentages, median (range), and mean values. Kaplan-Meier survival analysis was used to estimate the median and mean OS time and to generate survival curves. Receiver operating characteristic (ROC) analysis was used to determine optimal cut-off values for markers and to perform sensitivity-specificity calculations. Cox regression assessed univariate survival risk, while multivariate models used the Forward Stepwise (Likelihood Ratio) method. A p-value less than 0.05 was considered statistically significant. Analyses were performed using SPSS v24 (SPSS Inc., Chicago, IL, USA).

Results

The study included 38 patients with HR+/HER2– breast cancer that was metastatic at the time of diagnosis. The median age at diagnosis was 59.50 years (range: 32–84 years). The majority of patients (71.1%, $n=27$) were over 60 years of age, and 78.9% ($n=30$) were postmenopausal. During the study period, 21 patients (55.2%) developed disease progression, while three patients (7.8%) died from breast cancer.

The optimal cut-off values for the PLR, NLR, CAR, and HALP score in predicting disease progression were assessed us-

ing ROC curve analysis. The ideal cut-off value for PLR was determined to be 128, with a sensitivity of 71.4%, specificity of 76.5%, area under the curve (AUC) of 0.786 (95% confidence interval [CI]: 0.638-0.934, $p=0.003$; Fig. 1). For the HALP score, the optimal cut-off was 32.6, with a sensitivity of 81.0%, specificity of 76.5%, AUC of 0.875 (95% CI: 0.766-0.985, $p=0.001$; Fig. 1). No significant cut-off values were identified for NLR (AUC: 0.587, 95% CI: 0.400-0.774, $p=0.363$) or CAR (AUC: 0.524, 95% CI: 0.331-0.717, $p=0.803$). The median NLR (2.35) and CAR (0.75) values were included in subsequent analyses.

Kaplan-Meier survival analysis estimated an OS time of 45 months (95% CI: 37.2-52.8). Premenopausal and perimenopausal patients demonstrated reduced survival compared to postmenopausal patients, with median OS times of 28.5 months versus 52.0 months, respectively (Fig. 2). Patients presenting with visceral metastases at diagnosis showed significantly shorter median OS (32.3 months) compared to those without visceral metastases (47.6 months; $p<0.001$; Fig. 2). Similarly, patients with CAR values <0.75 exhibited

longer OS (47.6 months) than those with $CAR \geq 0.75$ (32.3 months; $p=0.002$; Table 1, Fig. 2).

Cox regression analysis revealed that postmenopausal patients had a 45.9% reduced mortality risk compared to premenopausal patients (hazard ratio [HR]: 0.541; 95% CI: 0.357-0.821; $p=0.004$). Patients with visceral metastases demonstrated a 14.2-fold increased mortality risk (HR: 14.255; 95% CI: 2.603-78.059; $p=0.002$). Furthermore, elevated CAR was associated with significantly higher mortality risk compared to lower CAR values (HR: 4.772; 95% CI: 1.593-14.295; $p=0.005$). No statistically significant associations were observed between mortality risk and age, progesterone receptor (PgR) status, Ki-67 index, tumor grade, presence of bone metastases, NLR, PLR, or HALP score (Table 2).

Multivariate modeling demonstrated significant associations for:

1. Menopausal status and visceral metastasis (HR: 0.513, 95% CI: 0.326-0.808, $p=0.004$; and HR: 18.078, 95% CI: 2.861-114.231, $p=0.002$, respectively)
2. Menopausal status and CAR (HR: 0.506, 95% CI: 0.322-0.795, $p=0.003$; and HR: 5.645, 95% CI: 1.752-18.192, $p=0.004$, respectively) (Table 3).

Discussion

This study evaluated the prognostic significance of pre-treatment inflammatory markers - PLR, NLR, CAR, and HALP score - in patients with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer receiving CDK4/6 inhibitors. Our findings demonstrate that visceral metastases and pre-/perimenopausal status at diagnosis correlate with poorer OS. To our knowledge, this represents both the first study identifying elevated CAR as a prognos-

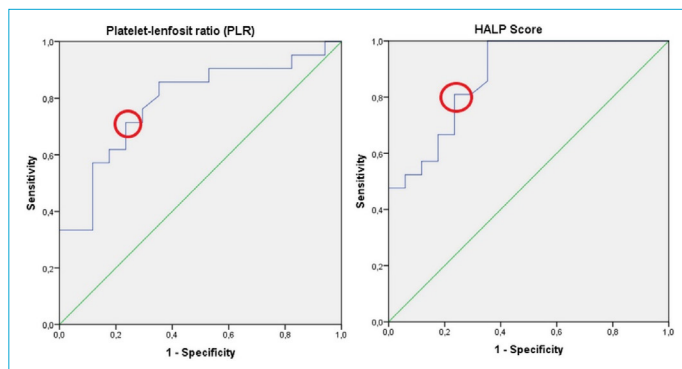


Figure 1. Receiver operating characteristic (ROC) curves for platelet-to-lymphocyte ratio (PLR) and Hemoglobin, Albumin, Lymphocyte, Platelet (HALP) Score R1Q4.

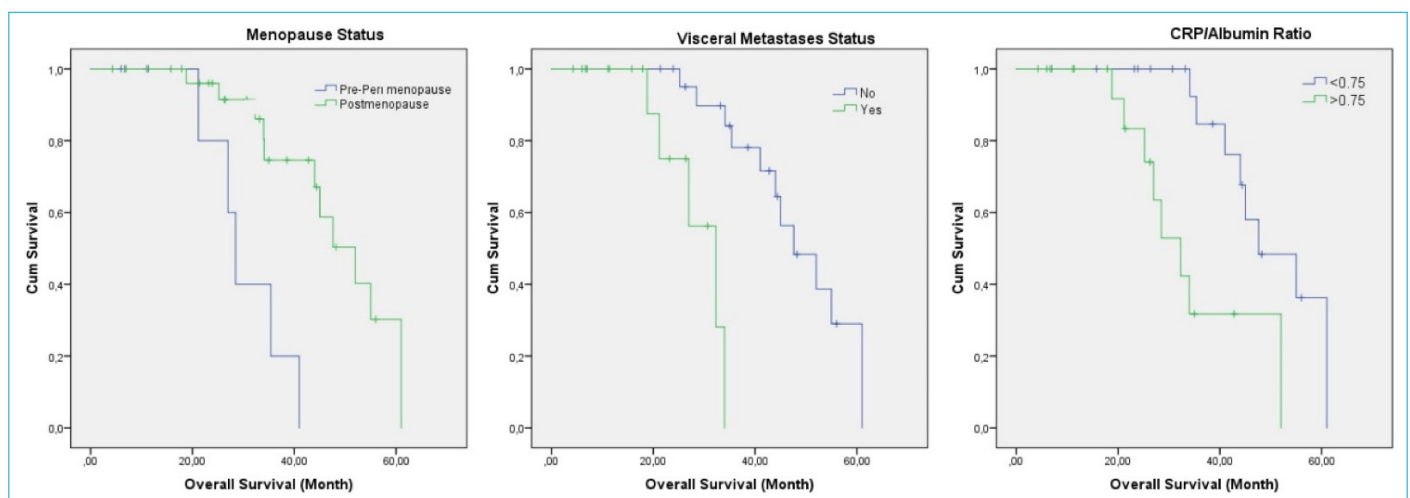


Figure 2. Menopause Status, Visceral Metastasis Status, C-reactive protein (CRP)/albumin ratio (CAR) Overall Survival Graphics.

Table 1. Clinical and laboratory data of patients and estimated median overall survival analyses

	n (38)	%	Median OS	p
Age				
<60	11	28.9	35.4	0.494
≥60	27	71.1	47.6	
PgR				
<20	10	26.3	47.6	0.215
≥20	28	73.7	44.0	
Ki67				
<30	14	36.8	52.0	0.155
≥30	24	63.2	44.0	
Grade				
Grade 1-2	26	68.4	45.0	0.318
Grade 3	12	31.6	27.0	
Menopause				
Pre-perimenopausal	8	21.1	28.5	0.001
Postmenopausal	30	78.9	52.0	
Visceral metastasis				
No	22	57.8	47.6	<0.001
Yes	16	42.1	32.3	
Bone metastasis				
No	10	26.3	61.0	0.058
Yes	28	73.7	41.0	
NLR				
<2.35	19	50.0	52.0	0.492
>2.35	19	50.0	44.0	
PLR				
<128	19	50.0	52.0	0.100
>128	19	50.0	35.4	
HALP Score				
<32.6	17	44.7	44.0	0.398
>32.6	21	55.3	52.0	
CAR				
<0.75	19	50.0	47.6	0.002
>0.75	19	50.0	32.3	

PgR: Progesterone receptor; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; CAR: C-reactive protein(CRP)/albumin ratio; HALP Score: Hemoglobin, Albumin, Lymphocyte, Platelet Score.

tic marker for diminished OS in stage IV breast cancer and the inaugural investigation simultaneously assessing all four biomarkers in the same patient cohort.

This study aimed to identify cost-effective and easily obtainable prognostic markers utilizing routine laboratory tests including complete blood count, serum albumin, and CRP levels - all standard components of pretreatment clinical evaluation. The utilization of such readily available biomarkers holds particular significance for clinical practice in resource-limited settings, where access to advanced molecular testing remains constrained. Notably,

Table 2. Univariate Cox-Regression analysis of variables for overall survival

Variable	Category	HR (95% CI)	p
Age	<60/≥60	0.728 (0.272-1.946)	0.527
PgR	<20/ ≥20	2.526 (0.556-11.480)	0.230
Ki67	<30/≥30	2.262 (0.714-7.168)	0.165
Grade	1-2/Grade 3	1.909 (0.525-6.935)	0.326
Menopause	Pre-peri/post	0.541 (0.357-0.821)	0.004
Visceral metastasis	No/Yes	14.255 (2.603-78.059)	0.002
Bone metastasis	No/Yes	2.721 (0.862-8.585)	0.088
NLR	<2.35/>2.35	1.432 (0.512-4.011)	0.494
PLR	<128/>128	0.393 (0.124-1.243)	0.112
HALP Score	<32.6/>32.6	0.604 (0.185-1.968)	0.403
CAR	<0.75/>0.75	4.772 (1.593-14.295)	0.005

PgR: Progesterone receptor; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; CAR: C-reactive protein(CRP)/albumin ratio; HALP Score: Hemoglobin, Albumin, Lymphocyte, Platelet Score.

Table 3. Multivariate Cox-regression models of variables

Model 1			
Variable	Category	HR (95% CI)	p
Menopauses	Pre-peri/post	0.513 (0.326-0.808)	0.004
Visceral metastasis	No/Yes	18.078 (2.861-114.231)	0.002
Model 2			
Variable	Category	HR (95% CI)	p
Menopause	Pre-peri/post	0.506 (0.322-0.795)	0.003
C-reactive protein (CRP)/albumin ratio	<0.75/>0.75	5.645 (1.752-18.192)	0.004

The forward Stepwise (Likelihood Ratio) method was used for the models.

mBC continues to demonstrate substantial heterogeneity in treatment responses and OS outcomes, persisting as an incurable disease entity despite recent therapeutic advancements.^[27]

Neutrophils contribute to immunosuppression within the tumor microenvironment through the secretion of pro-inflammatory cytokines and inhibition of T-cell-mediated cytotoxicity. In contrast, lymphocytes demonstrate antitumor activity via direct cytotoxic effects on malignant cells, while platelets promote tumor progression by facilitating metastatic invasion and angiogenesis through paracrine signaling.^[28] This complex interplay of inflammatory processes underscores the critical role of tumor-associated inflammation in breast cancer pathogenesis, from initial tumorigenesis to disease progression and ultimate clinical outcomes. Consequently, systemic inflammatory markers, particularly the NLR and PLR, have emerged as clinically relevant prognostic indicators across multiple cancer types.^[26]

CRP represents a highly sensitive biomarker of systemic inflammation and tissue damage, demonstrating variable elevation across different cancer types and disease stages.^[29] As an acute-phase reactant, CRP synthesis is upregulated by proinflammatory cytokines, particularly interleukin-6 (IL-6), during inflammatory responses.^[30, 31] Conversely, serum albumin levels serve as a reliable indicator of nutritional status, with characteristic hypoalbuminemia in cancer patients resulting from both chronic inflammation-mediated catabolism and cancer-associated malnutrition.^[30] Similarly, anemia, as reflected by reduced hemoglobin concentrations, frequently manifests in oncologic patients through multifactorial mechanisms including nutritional deficiencies, occult bleeding, and anemia of chronic disease mediated by inflammatory cytokine networks.^[32]

Collectively, these findings demonstrate that the HALP score and CAR, as composite biomarkers integrating hemoglobin, lymphocyte, platelet, and albumin measurements, provide clinically relevant indices for evaluating both nutritional status and systemic immune competence in cancer patients.

Despite the strong theoretical rationale supporting these inflammatory biomarkers, their clinical implementation faces substantial challenges due to significant inter-patient variability and methodological inconsistencies across laboratories. This heterogeneity manifests as divergent cutoff values and conflicting results in the existing literature.^[33] While the HALP score has demonstrated prognostic potential in multiple studies, its translation into routine clinical practice remains uncertain due to unresolved questions regarding optimal implementation protocols.^[32] Furthermore, the absence of standardized reference ranges for these indices in healthy populations complicates their interpretation in clinical settings.^[30] Consequently, although numerous inflammation-based prognostic markers have been proposed for breast cancer, no consensus exists regarding the most clinically relevant parameter, highlighting the need for further validation studies.^[31]

The investigation by Moukas et al. represents one of the few studies to examine these inflammatory parameters in metastatic breast cancer patients receiving first-line CDK4/6 inhibitor therapy. Their results demonstrated that elevated NLR possesses prognostic significance, showing an inverse correlation with OS.^[19] While our analysis did not reach statistical significance for this association, we observed a consistent trend toward reduced survival in patients with higher NLR values. Complementary findings by Duran et al. established that lower HALP scores correlate with more aggressive tumor biology, manifested through advanced tumor stage and axillary lymph node involvement.^[21] Parallel observations by Krenn-Pilko et al. revealed a statistically significant relationship between increased PLR and worse OS outcomes.^[14] Although our study failed to confirm the

prognostic value of either low HALP scores or elevated PLR at statistically significant levels, the numerical trends in our data consistently mirrored these previously reported associations with poorer survival outcomes.

The study by Iztuegbuna et al.^[34] established the CAR as a reliable indicator of nutritional status in breast cancer patients. Supporting evidence from Liu et al.^[29] demonstrated that preoperative CAR levels significantly correlated with survival outcomes, suggesting its potential utility as a prognostic marker specifically in luminal B subtype breast cancer. Complementary findings by Zhou et al.^[22] further validated these observations, showing that elevated preoperative CAR levels were significantly associated with improved both disease-free survival (DFS) and OS.

Our current investigation extends these findings by demonstrating that elevated pretreatment CAR may serve as an independent adverse prognostic factor in breast cancer patients. While our study represents the first focused analysis in a stage IV HR+/HER2- cohort, the results remain consistent with existing literature across diverse breast cancer populations. However, the limited number of comparable studies underscores the need for additional validation studies and clinical feasibility assessments to fully elucidate the prognostic role of these inflammatory markers.

Limitations

While this study provides meaningful contributions to the existing literature, it has some limitations. First, the retrospective design inherently limits control over data collection and introduces potential confounding variables. Second, the relatively short follow-up period may not fully capture long-term clinical outcomes. Third, the modest sample size ($n=38$) reduces statistical power and may limit generalizability of the findings. While these results require validation in larger prospective cohorts, they nevertheless provide compelling preliminary evidence supporting further investigation. Additionally, although we carefully excluded known confounding factors affecting laboratory parameters, the retrospective nature of the study precludes complete control over all potential variables influencing inflammatory marker measurements.

Conclusion

In conclusion, our findings demonstrate that the CAR can be a clinically viable, cost-effective prognostic biomarker for patients with advanced breast cancer undergoing CDK4/6 inhibitor therapy. The simplicity, accessibility, and reproducibility of CAR measurement make it particularly valuable for routine clinical practice. These results provide a foundation for future large-scale, multicenter prospective studies to further validate CAR's prognostic utility and establish standardized implementation protocols in diverse patient populations.

Disclosures

Author Contributions: Conceptualization: S.S.; Data curation: S.S. and H.K.; Formal analysis: S.S.; Funding acquisition: S.S.; Investigation: S.S.; Methodology: S.S.; Project administration: S.S.; Resources: S.S.; Software: S.S.; Supervision: S.S.; Validation: S.S.; Visualization: H.K.; Writing – original draft: S.S.; Writing – Review & editing: S.S.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (or Ethics Committee) of Balikesir Ataturk State Hospital (protocol code 2025/03/2025 and approval date: 20/03/2025).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the written informed consent was obtained from the patients (s) for publication of this paper.

Data Availability Statement: Although not publicly available, the datasets created and/or analyzed during the current study are available from the corresponding author upon justifiable request.

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

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