Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1268419

Prognostic significance of systemic immune inflammation indices and prognostic nutritional index before CDK4/6 inhibitor therapy in hormone receptor positive, HER2 negative metastatic breast cancer patients

Hormon reseptör pozitif, HER-2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesi sistemik immün inflamasyon indekslerinin ve prognostik nutrisyonel indeksin prognostik önemi

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Received:18.04.2023 Accepted:21.08.2023

Abstract

Purpose: As systemic inflammatory indices and prognostic nutritional index are associated with poor prognosis in many tumor types, the goal of the present study was to ascertain their effect along with the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, C-reactive protein/albumin ratio, and systemic inflammatory response index on the progression-free survival (PFS) and overall survival (OS) of hormone receptor-positive HER2-negative (HR+/HER2−) metastatic breast cancer patients before CDK4/6 inhibitor treatment.

Materials and methods: The medical records of 79 patients with HR+/HER2− metastatic breast cancer who presented at the Medical Oncology Outpatient Clinic between January 2018 and May 2022 were retrospectively analyzed to gather relevant data measured before CDK4/6 inhibitor treatment in order to establish the effect of key markers on their PFS and OS.

Results: The median age of the participating patients, 70 (88.6%) of whom were postmenopausal, was 53 years (range 26-80 years). While 68 patients (86.1%) had a 0 performance score, 10 (12.7%) developed metastases during adjuvant endocrine therapy. Factors affecting PFS were age <50 (p=0.061), metastasis development during adjuvant endocrine therapy (p=0.09) and C-reactive protein/albumin ratio (p=0.019), while OS was primarily influenced by age <50 (p=0.069) and metastasis development during adjuvant endocrine therapy (p=0.012).

Conclusion: In the examined HR+/HER2− metastatic breast cancer patients, systemic inflammatory indices and prognostic nutritional index before CDK4/6 inhibitor treatment affected PFS. In addition, metastasis development during adjuvant endocrine therapy, progesterone receptor percentage, and age below 50 years emerged as prognostic factors for shorter overall survival.

Keywords: HR+/HER2− metastatic breast cancer, CDK4/6 inhibitors, systemic inflammatory indices, prognostic nutritional index, PFS.

Cakan Demirel B, Yaren A, Demiray AG, Yapar Taskoylu B, Dogan T, Ozdemir M, Guclu Kantar T, Karan C, Degirmencioglu S, Gokoz Dogu G. Prognostic significance of systemic immune inflammation indices and prognostic nutritional index before CDK4/6 inhibitor therapy in hormone receptor positive, HER2 negative metastatic breast cancer patients. Pam Med J 2024;16:682-695.

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Öz
Amaç: Sistemik inflamatuvar indeksler ve Prognostik nutrisyonel indeks birçok tümör tipinde kötü prognoz ile ilişkilidir. Çalışmamızda hormon reseptörü pozitif HER2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesinde sistemik inflamatuar indeksi, prognostik nutrisyonel indeks, Nötrofil/Lenfosit oranı, Platelet/Lenfosit oranı, Lenfosit Monosit Oranı, C-reaktif protein/albümin oranı, sistemik inflamatuar yanıt indeksi gibi belirteçlerin progresyonsuz sağkalım ve tüm sağkalım üzerine etkisi araştırıldı.
Gereç ve yöntem: Ocak 2018-Mayıs 2022 tarihleri arasında Tıbbi Onkoloji polikliniğe başvuran hormon reseptörü pozitif HER2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesi hastaların verileri retrospektif olarak incelendi. Bu belirteçlerin progresyonsuz sağkalım ve total sağkalım üzerine etkisi araştırıldı.
Bulgular: Çalışmaya 79 hasta dahil edildi. Hastaların ortanca yaşları 53 (aralık 26-80 yıl) idi. Yetmiş hasta (%88,6) postmenopozaldı. Hastaların 68'inin (%86,1) performans skoru 0'dı. Adjuvan endokrin tedavi sırasında 10 hastanın (%12,7) metastazı gelişti. PSK'yi etkileyen faktörler; yaş <50 (p=0,061), adjuvan endokrin tedavi sırasında metastaz gelişmesi (p=0,09) ve C-reaktif protein/albümin oranı (p=0,019) iken; TSK'ı etkileyen faktörler; yaş <50 (p=0,069) ve adjuvan endokrin tedavi sırasında metastaz gelişmesi (p=0,012) olarak bulundu.
Sonuç: Hormon reseptörü+/HER2 – metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisinden önce hastaların sistemik inflamatuvar indeksleri ve prognostik nutrisyonel indeksi progresyonsuz sağkalımı etkilemektedir. Ayrıca hastalarda adjuvan endokrin tedavi sırasında metastaz gelişmesi, progesteron reseptör yüzdesi ve 50 yaşın altı olması tüm sağkalım için olumsuz prognostik faktörler olarak değerlendirildi.

Anahtar kelimeler: HR+/HER2- meme kanseri, CDK4/6 inhibitörü, sistemik inflamatuar indeksler, prognostik nutrisyonel indeks, PSK.

Çakan Demirel B, Yaren A, Demiray AG, Yapar Taşköylü B, Doğan T, Özdemir M, Güçlü Kantar T, Karan C, Değirmencioğlu S, Gököz Doğu G. Hormon reseptör pozitif, HER-2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesi sistemik immün inflamasyon indekslerinin ve prognostik nutrisyonel indeksin prognostik önemi. Pam Tıp Derg 2023;16:682-695.

Introduction

Breast cancer is the most common cancer in women and is the second leading cause of mortality after lung cancer [1]. In the molecular classification of breast cancer, the hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2−) group accounts for 60-65% of all breast cancers [2]. Endocrine therapy is the first-line treatment for women affected by HR+/HER2− metastatic breast cancer that have not experienced visceral crisis [3, 4]. However, only 20-40% of patients respond to aromatase inhibitors and 50% relapse within the first 8-14 months [5]. Therefore, due to the resistance to single-agent endocrine therapy, combination treatment strategies are increasingly being offered. As cyclin-dependent kinases (CDKs) are members of the serine/threonine kinase family that play a role in the regulation of the cell cycle [6], they have been shown to improve long-term survival when incorporated into the endocrine therapy [7-9]

The most important factors that play a role in the breast cancer prognosis are estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki-67 percentage. It is known that neutrophils, platelets and lymphocytes, which play a role in the immune system and inflammation, contribute to tumor invasion, patient survival, and the development of distant organ metastases [10, 11].

In addition, the prognostic importance of ratios such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), and C-reactive protein/albumin ratio (CAR), as well as indices such as systemic inflammatory index (SII), systemic inflammatory response index (SIRI), and prognostic nutritional index (PNI) has been demonstrated in many tumor types [12-16]. For example, in a meta-analysis investigating the prognostic significance of NLR in breast cancer, higher NLR was associated with shorter PFS and OS [17]. Moreover, a meta-analysis of preoperative breast cancer patients indicated presence of a negative correlation between low LMR and incident-free survival [18]. Likewise, extant evidence shows that neoadjuvant breast cancer patients with high PNI had longer DFS and OS than those with low PNI [19].

However, the effects of these prognostic indices on the survival in patients with HR+/HER2− metastatic breast cancer receiving CDK4/6 inhibitor treatment has never been investigated. This gap in extant literature is

addressed in the present study by examining whether the SII, PNI, NLR, PLR, LMR, CAR, and SIRI values before the CDK4/6 inhibitor treatment influence the survival (PFS and OS) in HR+/HER2− metastatic breast cancer patients, and whether these parameters can be used as prognostic markers in clinical practice.

Materials and methods

Following the approval by the Pamukkale University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee, medical files of HR+/HER2− metastatic breast cancer patients who attended the Pamukkale University Medical Oncology Outpatient Clinic between January 2018 and May 2022 prior to commencing CDK4/6 treatment were retrospectively analyzed and pertinent data was recorded. The study sample included 79 female patients aged 18-80 years, who were pathologically diagnosed with invasive ductal carcinoma, ECOG PS 0-1, HER2− with ER and/or PR >1%, without evidence of visceral crisis, and who subsequently received CDK4/6 inhibitor with endocrine therapy. Age, menopausal status, previous treatments, ECOG performance status, ER, PR and Ki-67 percentages, number of metastases, and metastasis locations were obtained from their files, while neutrophil, lymphocyte, monocyte, platelet, CRP and albumin levels were obtained from their hemogram panels stored in the Hospital Laboratory Information System. Hemogram parameters were analyzed by electrical impedance and optical density method using Mindray CAL 8000 (Shanghai, China) auto analyzer, while CRP and albumin levels were established via electrochemiluminescence method in Cobas 702 (Roche Diagnostics, Manheim, Germany) analyzers. The obtained values were used to calculate PNI, SII, NLR, PLR, LMR, CAR and SIRI based on the following formulae:

PNI = serum albumin level (g/dL) × 10+lymphocyte count (/nL) × 0.005

SII = platelet count × neutrophil count / lymphocyte count

NLR= neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

LMR = lymphocyte count/monocyte count

CAR = C-reactive protein/albumin level

SIRI = neutrophil count × monocyte count/ lymphocyte count

Overall survival (OS) was defined as the time that elapsed from the date of metastasis diagnosis until mortality, whereas progression-free survival (PFS) was defined as the time period from the date of metastasis diagnosis until disease progression.

Statistical analyses

Mann-Whitney U and Chi-squared or Fisher's exact test were used to determine the values and percentages of clinicopathological parameters. The PNI, SII, NLR, PLR, LMR, CAR and SIRI threshold values were established through Receiver operating characteristic (ROC) analysis, and Kaplan-Meier and log rank analysis were conducted to obtain PFS and OS values. Univariate and multivariate analyses were performed using Cox proportional hazards model, whereby hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were recorded for each factor. All analyses were performed using SPSS (version 23.0) software package (SPSS Inc., Chicago, IL, USA) and $p<0.05$ was considered statistically significant.

Results

The data of 79 female patients (median age 53 years, range 26-80 years) with metastatic HR+/HER2− invasive ductal carcinoma without visceral crisis obtained before CDK4/6 inhibitor + endocrine therapy was evaluated. As shown in Table 1, the sample comprised of 70 (88.6%) postmenopausal patients, 68 (86.1%) patients with ECOG 0 performance status, and 10 (12.7%) patients who developed metastasis during adjuvant endocrine therapy. Moreover, 15 (19%) patients had a single metastatic region, while ≥5 metastatic regions were noted in 54 (68.4%) cases. There were 25 (31.6%) patients with only bone metastases, while 30 (38.0%) had visceral metastases (but none experienced visceral crisis).

ROC analysis was performed to obtain the PNI, SII, NLR, PLR, LMR, CAR and SIRI

Table 1. Patient characteristics

	n	%
Age		
>50 years	45	57
≤50 years	34	43
Performance status 0	68	86.1
1	11	13.9
Menopausal status		
Postmenopausal	70	88.6
Premenopausal	9	11.4
Metastasis region		
Bone	25	31.6
Visceral	30	38.0
Both	24	30.4
Metastasis count		
Single	15	19.0
2	5	6.3
3	5	6.3
≥4	54	68.4
Treatment type		
Palbociclib+Letrazole	15	19.0
Ribociclib+Letrazole	33	41.8
Palbociclib+Fulvestrant	15	19.0
Ribociclib+Fulvestrant	16	20.2
Treatment before CD4/6 inhibitor		
Received	44	55.7
Not Received	35	44.3
Treatment before CD4/6 inhibitor		
1st line	12	15.2
2nd line	14	17.7
3rd line and onwards	18	22.8
CD4/6 treatment response		
Progression	18	22.8
No Progression	61	72.2
Patient's last condition		
Alive	68	86.1
Deceased	11	13.9

threshold values on the basis of pertinent laboratory findings and the results are reported in Table 2, along with the AUC, *p* values, and 95% CIs. As can be seen from the tabulated data, the threshold value for PNI was 48.65 (sensitivity 55.6%, specificity 77%); the threshold value for SII was 718637.6 (sensitivity 61.1%, specificity 67%); the threshold value for SIRI was 1134.9 (sensitivity 66.1%, specificity 62.7%); the threshold value for PLR was 184. 9 (sensitivity 66.7%, specificity 73.8%); the threshold for CAR was 2.14 (sensitivity 72.2%, specificity 78.7%); the threshold for NLR was 2.68 (sensitivity 61.1%, specificity 70.5%); and the threshold value for LMR was 3.4 (sensitivity 72%, specificity 69%).

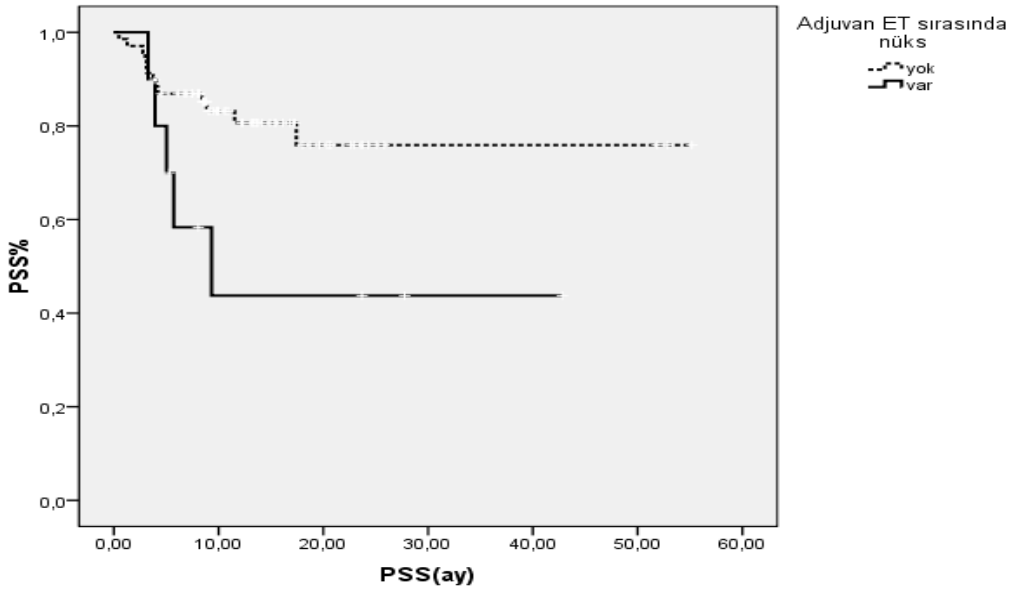
Table 2. ROC analysis values

Values	AUC	SE	*P* value	95% Confidence Interval
SII (718 637.6)	.637	.075	.080	.489
SIRI (1134.9)	.673	.077	.026	.521
PNI* (48.65)	.629	.078	.098	.476
PLR (184.9)	.682	.076	.019	.532
CAR (2.14)	.759	.069	.001	.623
NLR (2.68)	.679	.070	.022	.542
LMR* (3.4)	.679	.079	.021	.524

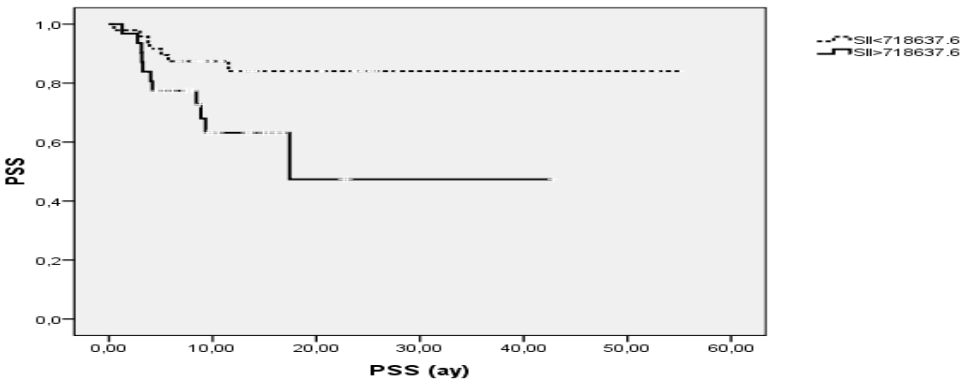
* Lower values in the ROC analysis indicate a positive test

For the examined cohort, the median follow-up was 66.2 months (11.3-308.4), while the median progression-free survival (mPFS) was 41.8+2.8 (95% CI 36.2-47.4) months, and the median overall survival (mOS) was 257.5+4.0 (95% CI 230.1-284.9) months. In addition, 18 (22.8%) patients progressed and 11 (13.9%) died during the investigated period. When the effect of clinicopathological and laboratory parameters on PFS was evaluated, metastasis development during adjuvant endocrine therapy (p=0.033), SII>718637.6 (p=0.01), SIRI>1134.9 (p=0.02), PNI<48.64 (p=0.006), PLR>184.9 (p=0.001), CAR>2.14 (p=0.000), NLR>2.68 (p=0.02) and LMR<3.4 (p=0.000) were found to adversely affect PFS duration Figure 1(a-h). Moreover, OS was shorter in patients with PR below 50% (p=0.028), those who developed metastases during adjuvant endocrine therapy (p=0.002), those that had PLR >184.9 (p=0.07) and those in whom CAR >2.14 was noted (p=0.09), as shown in Table 3, Figure 2(a-d).

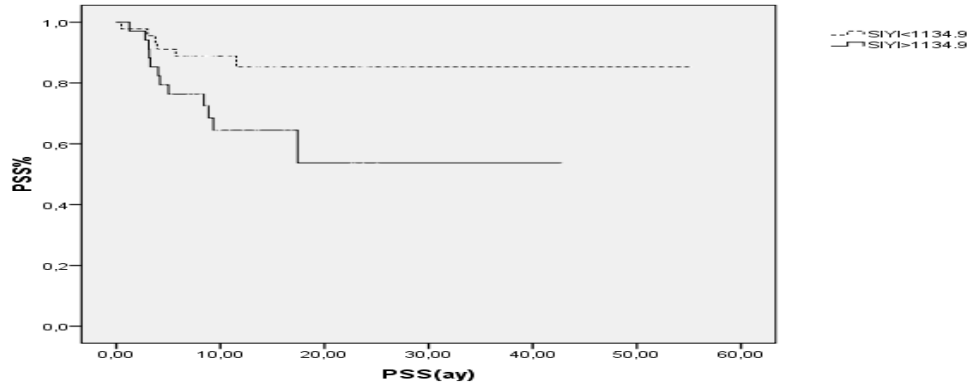
The findings yielded by the Cox proportional hazards model identified age <50 (p=0.061), metastasis development during adjuvant endocrine therapy (p=0.09) and CAR (p=0.019) as the factors affecting PFS (Table 4), while OS was influenced by age <50 years (p=0.069) and metastasis development during adjuvant endocrine therapy (p=0.012) (Table 5).



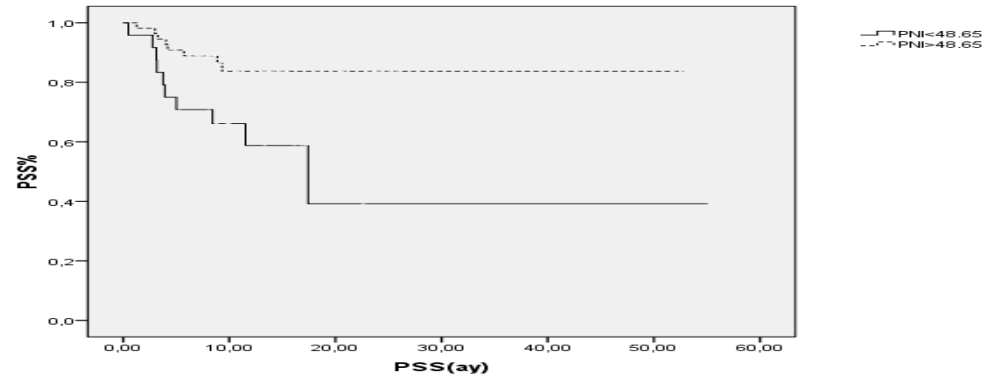
a. Presence of recurrence during adjuvant treatment (p=0.033)



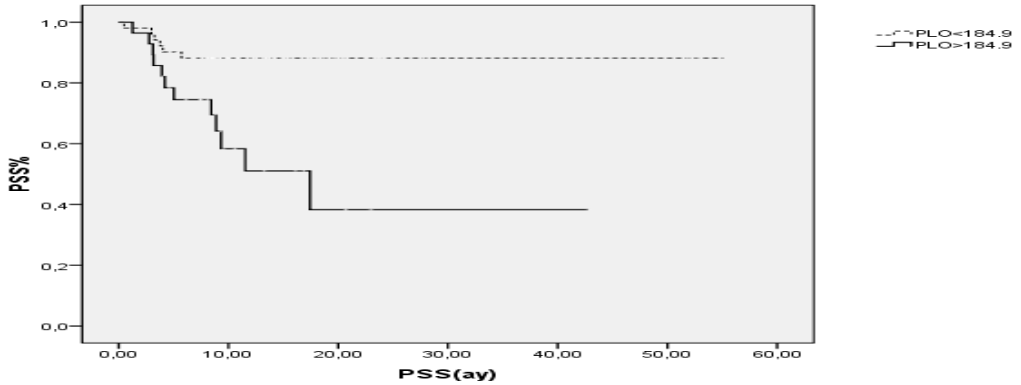
b. SII>718637.6 (*p*=0.01)



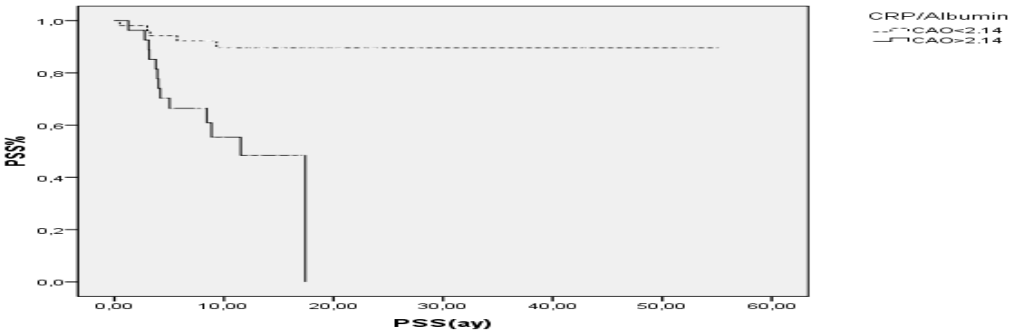
c. SIRI>1134.9 (*p*=0.02)



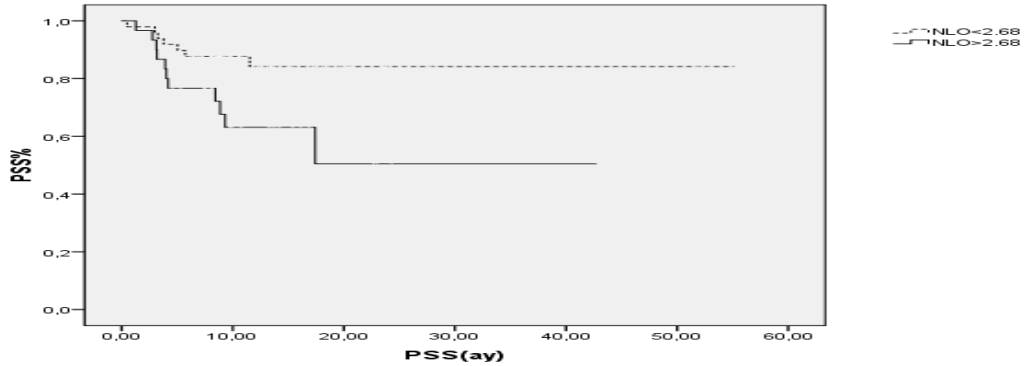
d. PNI<48.64 (*p*=0.006)



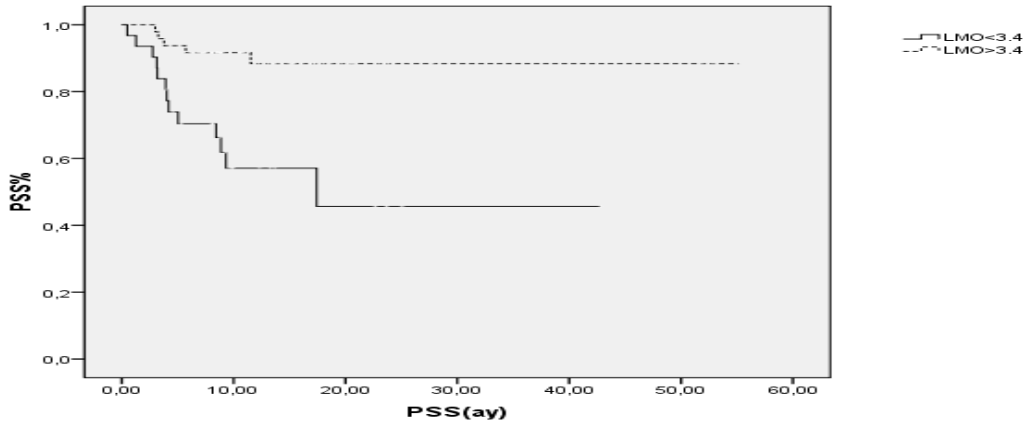
e. PLR>184.9 (*p*=0.001)



f. CAR>2.14 (*p*=0.000)



g. NLR>2.68) (*p*=0.02)

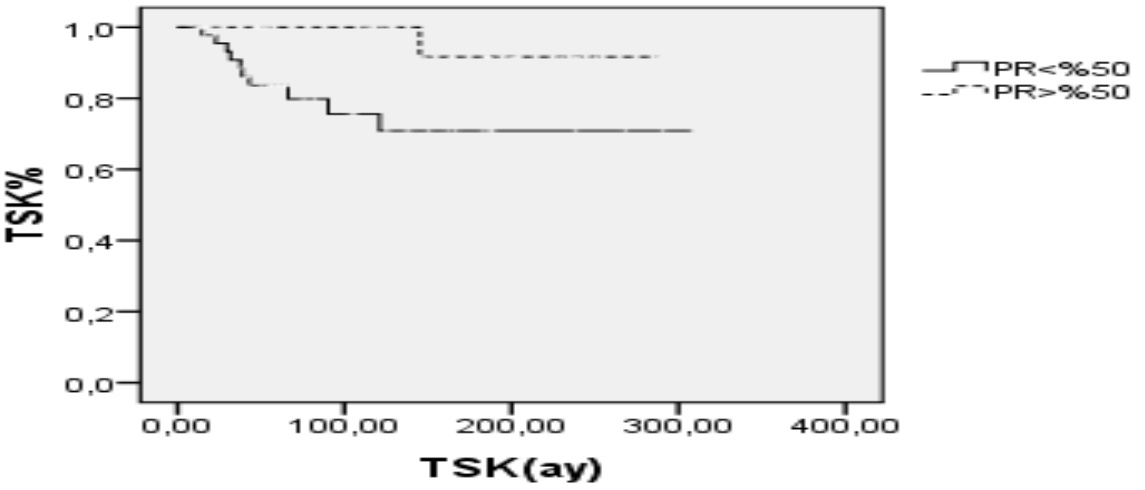


h. LMR<3.4 (*p*=0.000)

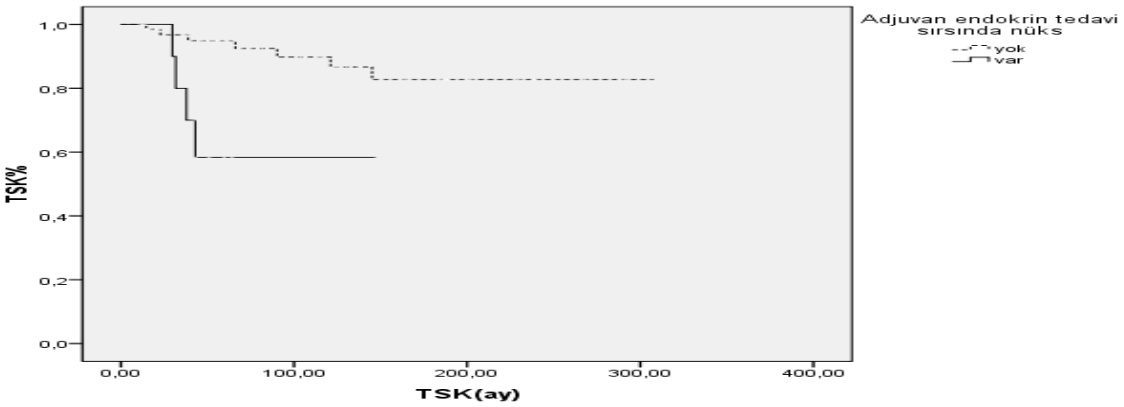
Figure 1. Kaplan Meier survival curves for factors affecting progression-free survival (PFS)

Table 3. PFS and OS values according to clinicopathological and laboratory values

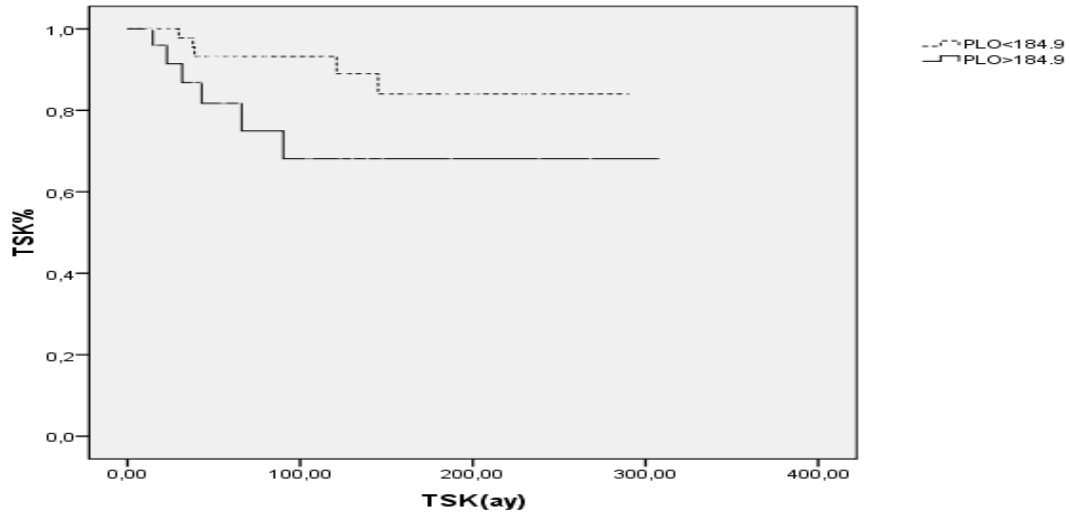
Parameters	Progression-free survival (months) (95%CI)	Overall survival (months) (95%CI)
Age ≤50 years (n=34)	34.6±5.3 (24.1-45.2)	247.9±2.8 (205.2-290.6)
Age >50 years (n=45)	44.7±2.8 (39.1-50.3) *p*=0.08	250.4±17.1 (217.1-283.8) *p*=0.49
ER <%50 (n=12)	41.7±6.7 (28.5-54.9)	251.4±25.7 (200.9-301.8)
ER ≥%50 (n=67)	40.3±2.9 (34.6-46.1) *p*=0.657	254.2±16.6 (221.5-286.8) *p*=0.71
PR <%50 (n=47)	39.5±3.6 (32.3–46.7)	235.7±20.1 (196.3-275.1)
PR ≥%50 (n=32)	41.5±4.7 (32.2-50.7) *p*=0.225	276.2±11.4 (253.8-298.5) *p*=0.028*
Ki67 <%20 (n=41)	44.3±3.4 (37.5-51.1)	255.7±21.5 (213.6-297.7)
Ki67 ≥%20 (n=38)	36.6±4.2 (28.2-44.9) *p*=0.444	242.6±16.7 (209.7-275.5) *p*=0.87
Metastasis during adjuvant endocrine therapy (n=10)	21.9+6.4 (9.4-34.5)	101.1±17.9 (65.8-136.2)
Metastatic at diagnosis (n=69)	43.7+2.9 (37.8-49.5) ***p*=0.033***	270.0±13.5 (243.5-296.4) ***p*=0.002***
SII <718637.6 (n=48)	47.2±2.7 (41.7- 52.7)	250.4±15.3 (220.4-280.4)
SII ≥718637.6 (n=31)	25.1±4.5 (16.1-33.9) ***p*=0.01***	249.4±23.6 (203.1- 295.6) *p*=0.428
SIRI <1134.9 (n=45)	47.8±2.8 (42.3-53.4)	241.5±18.3 (205.5-277.6)
SIRI ≥1134.9 (n=34)	26.7±3.8 (19.2-34.3) ***p*=0.02***	261.1±19.4 (223.0- 299.1) *p*=0.100
NLR <2.68 (n=49)	47.3±2.8 (41.8-52.7)	247.3±16.4 (215.2-279.4)
NLR ≥2.68 (n=30)	25.8±4.2 (17.7-34.0) ***p*=0.02***	253.2±22.2 (209.6- 296.7) *p*=0.65
PLR ≥184.9 (n=28)	21.7±4.4 (13.2-30.3)	226.0±28.5 (170.2- 281.8)
PLR <184.9 (n=51)	49.1±2.3 (44.4-53.6) ***p*=0.001***	259.4±13.3 (233.4-285.5) *p*=0.07
LMR ≤3.4 (n=31)	23.6±4.1 (15.6-31.6)	242.7±23.4 (196.8-288.6)
LMR >3.4 (n=48)	49.5±2.4 (44.7-54.3) ***p*=0.000***	233.6±14.3 (205.5- 261.6) *p*=0.36
PNI <48.65 (n=24)	27.2±7.3 (12.9-41.5)	244.9±24.9 (196.1-293.9)
PNI ≥48.65 (n=55)	45.1±2.5 (40.2-50.1) ***p*=0.006***	227.4±15.0 (198.2- 256.8) *p*=0.410
CAR <2.14 (n=52)	49.9±2.2 (45.5-54.3)	257.1±14.2 (229.4-284.8)
CAR ≥2.14 (n=27)	11.4±1.3 (8.7-14.0) ***p*=0.000***	232.5±26.7 (180.1- 284.8) *p*=0.09



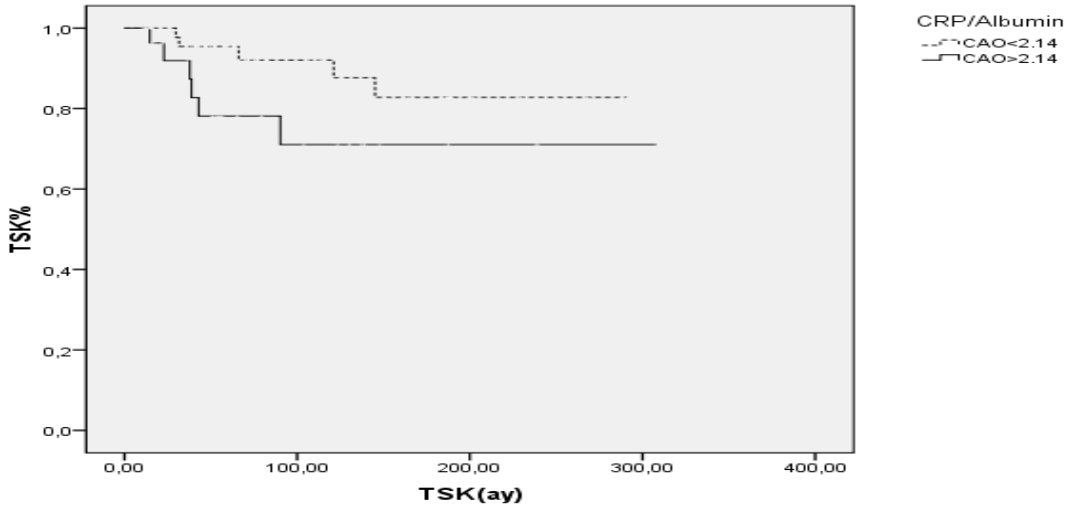
a. PR<%50 (*p*=0.028)



b. Recurrence during adjuvant treatment (p=0.002)



c. PLR >184.9 (p=0.07)



d. CAR >2.14 (p=0.09)

Figure 2. Kaplan Meier Survival curves for factors affecting overall survival (OS)

Table 4. Cox Proportional Hazard Model for progression-free survival (PFS)

Variables in the Equation								
							95.0% CI for Exp (B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Adjuvan ET met	-1.058	.631	2.813	1	.093	.347	.101	1.195
SII	-.583	.929	.394	1	.530	.558	.090	3.450
SIRI	.776	.885	.769	1	.380	2.173	.384	12.304
PNI	.049	.615	.006	1	.936	1.051	.315	3.506
PLR	-.723	.602	1.442	1	.230	.485	.149	1.579
CAR	-1.563	.669	5.456	1	.019	.210	.056	.778
NLR	.318	.823	.149	1	.699	1.374	.274	6.895
LMR	1.038	.778	1.780	1	.182	2.823	.615	12.964
Age	-.038	.020	3.497	1	.061	.963	.925	1.002

Table 5. Cox Proportional Hazard Model for overall survival (OS)

Variables in the Equation								
							95.0% CI for Exp (B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Adjuvan ET met	-2.054	.816	6.329	1	.012	.128	.026	.635
SII	-.691	1.049	.433	1	.510	.501	.064	3.919
SIRI	.495	1.012	.239	1	.625	1.640	.226	11.914
PNI	.312	.844	.136	1	.712	1.366	.261	7.144
PLR	-.927	.935	.984	1	.321	.396	.063	2.471
CAR	-1.188	.920	1.666	1	.197	.305	.050	1.851
NLR	1.472	1.256	1.373	1	.241	4.356	.372	51.054
LMR	.074	1.101	.005	1	.946	1.077	.125	9.308
Age	.013	.029	.209	1	.647	1.013	.957	1.073
PR%	2.676	1.470	3.315	1	.069	14.526	.815	258.858

Discussion

In our study involving 79 HR+/HER2− metastatic breast cancer patients, metastasis development during adjuvant endocrine therapy, as well as high SII, SIRI, PLR, CAR and NLR, and low PNI and LMR, were found to affect PFS. Factors influencing the overall survival were PR <50%, metastasis development during adjuvant endocrine therapy, high PLR and CAR >.

These findings are supported by the available evidence, indicating that SII—as a new inflammatory marker calculated using neutrophil, platelet and lymphocyte counts in peripheral blood—can be utilized as a prognostic factor in many tumor types [20-22]. In a meta-analysis conducted by Ji and Wang [23], high SII was found to be associated with adverse prognosis in patients with gynecological and breast cancer. When the available data was segregated by tumor type and race, the significant relationship with HCC and PFS remained. The authors further noted that patients with high SII had shorter OS duration. In patients with breast cancer receiving neoadjuvant treatment, Chen et al. [24] found that SII exhibited similar relationship with PFS and OS. On the other hand, in the present study, in the group without lymphovascular invasion, more frequent recurrence was associated with higher SII. However, thus far, no investigation has been conducted to ascertain the prognostic importance of SII in patients with HR+/HER2− metastatic breast cancer using CDK4/6 inhibitors. This shortcoming was addressed in the current study, in which high SII was associated with shorter PFS duration.

SIRI is another systemic inflammatory marker that plays an important role in the prognosis of many malignant tumors [25-27], prompting research into its relevance in breast cancer. In a study conducted by Hua et al. [27] including preoperative postmenopausal breast cancer patients examining the prognostic effect of SIRI, although the duration of HCC was shorter in patients with high SIRI, it was not statistically significant. However, high SIRI was correlated with shorter OS. On the other hand, Jiang et al. [28] investigated the prognostic significance of SIRI and LMR in breast cancer patients receiving neoadjuvant treatment, and noted that SIRI was a better prognostic factor than LMR. Still, the prognostic significance of SIRI in patients with metastatic breast cancer has never been investigated, making our finding

that high SIRI exerts a negative effect on PFS in metastatic HR+/HER2− patients using CDK4/6 inhibitors highly pertinent.

The prognostic nutritional index (PNI) is calculated using serum albumin level and total lymphocyte count. Although PNI has been frequently used to determine the treatment effect and survival in cancers of the gastrointestinal tract (such as colorectal cancer or hepatocellular cancer), its prognostic value has recently been demonstrated in other cancer types [29-31]. In contrast to other inflammatory markers, lower PNI was associated with worse prognosis, as well as shorter OS and DFS durations. In their study involving 785 patients, Chen et al. [19] aimed to ascertain whether PNI could be a prognostic marker in patients with neoadjuvant breast cancer and established a PNI threshold value of 51. The authors further noted that breast cancer patients with high PNI had longer HSK and OS than those with low PNI. In addition, Hua et al. [32] investigated the prognostic importance of PNI in patients with T1-2 N1 breast cancer and its potential as a predictor for guiding radiotherapy. Their patients were segregated into four groups and the PNI threshold value was 52. In the high-PNI group, the five-year survival rate was 94.9%, but declined to 87.3% in the low-PNI group. In addition, when survival in patients with T1-2 N1 breast cancer receiving radiotherapy was assessed in relation to PNI, the high-PNI group had a significantly longer OS than the low-PNI group (p=0.033; Hazards ratio [95% CI]=0.175 [0.035-0.868]). Although in extant research different threshold values were determined by ROC analyses, regardless of the threshold value, the general conclusion was that PNI has an effect on OS and PFS. In a study involving metastatic breast cancer patients using eribulin conducted by Zhu et al. [33], after multiple-line treatment, PNI was shown to be an independently associated with OS.

As PLR is an important proinflammatory marker, its effect on cancer prognosis has been extensively investigated. In a retrospective study conducted by Anwar et al. [34], the effect of PLR on PFS and metastasis development was found to be statistically insignificant. However, in our study, PLR above the threshold value determined by ROC analysis (>184.9) was found to be associated with shorter PFS. The differences in the obtained results likely arise due to the different threshold values, as well as the number of patients evaluated and the type of metastatic disease. Therefore, further studies with a larger number of patients are needed to resolve these inconsistencies. Anwar et al. [34] also established that shorter PFS and shorter duration of distant metastatic disease development were associated with higher NLR. In our cohort, those with higher NLR had shorter PFS. Similarly, based on their meta-analysis including 32 studies and 8.215 advanced cancer patients, Li et al. [13] found that higher PLR was associated with shorter OS and PFS.

CRP, which is an important acute phase reactant in infection and inflammation, is synthesized by the liver. As albumin is a protein involved in inflammation and has many functions in circulation, it has been subject to considerable body of research, indicating that CRP/albumin ratio (CAR) has negative effects on the quality of life and treatment efficacy in many cancers [35, 36]. Similarly, following their large-scale observational study involving large group of patients with different cancer types, Zhu et al. [37] concluded that only CRP and its increase and decrease patterns can predict malignancy. In Zhou et al. [38] retrospective study examining the prognostic impact of CAR in patients with non-metastatic breast cancer, multivariate analysis showed that high CAR was an independent risk factor for long-term outcome, as well as predicted short PFS and OS. However, CAR in HR+/HER2− metastatic breast cancer patients receiving CDK4/6 inhibitor treatment has never been studied. In our cohort, although CAR showed a similar relationship with PFS in patients with metastatic HR+/HER2− breast cancer, there was no statistically significant relationship with OS.

LMR has been analyzed as a prognostic factor in many cancer groups, and the findings suggest that low LMR may be associated with shorter PFS and OS. In a study conducted by Zhang et al. [39], in which the prognostic effect of LMR was analyzed in 938 patients with stage 1-3 breast cancer, low LMR was associated with more adverse prognosis. When the patients were segregated into the HR+, HR− and HER2− groups, low LMR was found to be a statistically significant predictor of HCC in the HER2− group only. As these findings do not align with the results obtained in the current study, there is

an evident need for more research involving much larger patient samples and longer follow-up periods to ascertain the prognostic value of LMR for OS.

Metastasis development while on adjuvant therapy was associated with shorter PFS and OS in our study, which is expected, as endocrine resistance (ER) is not uncommon in patients with hormone-positive breast cancer and may have multiple causes. For example, up to 30% of metastatic ER-positive breast cancers may have activating mutations in the estrogen-binding domain of the gene encoding ER (ESR1) [40]. Resistance to endocrine therapy may be de novo or acquired during treatment. Moreover, loss of estrogen dependence can be due to loss of ER, or can arise even when ER positivity persists. However, patients can also develop resistance to a specific therapy, although the tumor is still estrogen dependent as a result of ESR1 mutations, signaling pathways of growth factor receptors, activation of pP13K/AKT/mTOR and RAF/MEK/ERK pathways, and/or changes in cell cycle checkpoints [41]. In a study conducted by Grasic Kuhar et al. [42], hormone positivity was found to be an independent prognostic factor for cancer recurrence and mortality in the second decade after surgery in patients with early stage breast cancer. In other words, hormone-positive patients usually experience late recurrence. Grasic Kuhar et al. [42] similarly found that OS of recurrent patients was significantly shorter than that measured for non-recurrent patients. In our study, both PFS and OS were short in patients who developed metastases during adjuvant treatment, which is expected and consistent with the findings reported in extant literature.

Overall, the cumulative evidence in this field suggests that PNI, SIRI, SII, LMR, CAR, and NLR, which are easy to evaluate in clinical practice, may have prognostic significance. In all studies that have focused on these prognostic markers, data was analyzed retrospectively. However, this is the first attempt to determine whether immune-inflammation indices and prognostic nutritional index can be used as prognostic factors in HR+/HER2− metastatic breast cancer patients receiving CDK4/6 inhibitor treatment. Although the number of patients was relatively small and the follow-up period was short, the findings are still valuable as they focus on a specific group of patients. Nonetheless, our results should be validated through additional investigations involving a larger number of patients and longer follow-up durations.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethics committee approval: Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study (number: E-60116787-020-277077, 09/09/2022 dated, 14 numbered board meeting).

Authors' contributions to the article

B.C.D and A.Y. constructed the main idea and hypothesis of the study. B.C.D. and A.Y. developed the theory and arranged/edited the material and method section. B.C.D., T.D., T.G.K., M.O., and C.K. have done the evaluation of the data in the results section. Discussion section of the article written by B.C.D., A.Y., A.G.D., B.Y.T., S.D. and G.G.D. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.