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Clinical Evaluation of Dynamic Monitoring of Neutrophil–to–lymphocyte and Platelet–to–lymphocyte Ratios in Primary Endocrine Therapy for Advanced Breast Cancer

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Abstract. *Background/Aim: The utility of peripheral blood neutrophil–to–lymphocyte ratios (NLRs) and platelet–to–lymphocyte ratios (PLRs) as prognostic predictors of surgery and chemotherapy in breast cancer has been reported. In this study, NLRs and PLRs were calculated before treatment and during cancer progression in primary hormone receptor-positive breast cancer (HRBC) patients who chose endocrine therapy (ET) as the primary treatment, and prognostic prediction and factor analysis were performed. Patients and Methods: A total of 55 patients diagnosed with stage IIIB, IIIC, or IV HRBC who received ET as the primary treatment were included. Results: Increased NLRs were found to significantly contribute to a shorter overall survival from cancer progression (OS-CP) (p=0.040, log-rank). Increased PLRs were similarly associated with a shorter OS-CP (p=0.036, log-rank). In multivariate analysis, an increased NLR was an independent prognostic factor (p=0.035, hazard ratio(HR)=5.221). Conclusion: Changes in NLRs and PLRs become prognostic indicators when the therapeutic effect of ET is limited.*

The usefulness of the peripheral blood neutrophil–to–lymphocyte ratio (NLR) as a prognostic predictor of the outcome of surgery and chemotherapy in breast cancer has been reported in a meta-analysis (1). Likewise, the peripheral blood platelet–to–lymphocyte ratio (PLR) has been reported to be useful for prognostic prediction in other meta-analyses (2, 3). Neutrophils resulting from inflammation produce ligands that induce proliferation of tumor cells and cytokines that induce angiogenesis (4-6). Platelets contain a large quantity of growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β, which affect tumor cells (7-11). Lymphocytes are responsible for the immune function of the host and inhibit the progression of cancer (12). That is, the immune microenvironment surrounding cancer contributes to cancer progression and metastasis, and NLRs and PLRs are good indicators reflecting the balance between the tumor-promoting environment and the antitumor immune status. We have previously reported on the correlation between NLRs or PLRs and prognosis in preoperative chemotherapy and endocrine therapy (ET) in breast cancer (13-15). However, in most previous reports, including ours, the evaluations were conducted prior to treatment that strongly influences NLR and PLR. However, since ET has little effect on peripheral blood, these ratios may reflect the tumor immune environment even after treatment has started.

Regarding the treatment of hormone receptor-positive breast cancer (HRBC) with distant metastasis, ET is often selected as the primary treatment when using the Hortobagyi algorithm (16). When the treatment effect of ET is reduced, it becomes necessary to change to another ET or chemotherapy. Recently, cyclin-dependent kinase (CDK) 4/6 inhibitors have been used clinically in patients with ET-resistant HRBC. However, there are no indicators to reliably determine when to switch from ET to chemotherapy.

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Therefore, we hypothesized that changes in NLR and PLR before and after ET as the primary treatment may be used to predict prognosis after first-line ET. In this study, NLRs and PLRs were calculated before treatment and at cancer progression in primary HRBC patients who chose ET as their primary treatment and further prognostic prediction and factor analysis were performed.

Patients and Methods

Patient background. HRBC patients diagnosed with stage IIIB, IIIC, or IV who received ET as the primary treatment at the Osaka City University Hospital from November 2007 to September 2017 were included in this study. All patients underwent a biopsy before treatment and were pathologically diagnosed with breast cancer. Classification into subtypes was performed using biopsy tissue that was subjected to immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki67. We defined patients with ER-positive and/or PgR-positive tumors as having HRBC. The stage of breast cancer was determined using ultrasonography (US), computed tomography (CT), and bone scintigraphy. Simultaneously duplicated cancer cases were excluded from this study. After the initiation of ET, all patients were followed up with physical and image examinations as necessary in the outpatient clinic. Within the follow-up period, cases in which the primary tumor was excised were excluded from this study. Therapeutic effects were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (17). Patients with clinical partial response (cPR) and clinical complete response (cCR) were defined as "Responders", and patients with clinical stable disease (cSD) and clinical progressive disease (cPD) were designated as "Non-responders" in the objective response rate (ORR). The day on which the therapeutic effect of the primary ET was evaluated as cPD was named "day-PD". Progression-free survival (PFS) was defined as the period from treatment initiation to the day-PD or death. The period from the day-PD to the time of death was named overall survival (OS) from cancer progression (OS-CP). The median follow-up period from the initiation of the primary ET was 1,075 days (range=214-3,379 days).

Blood sample analysis. Peripheral blood was analyzed before treatment and on day-PD. The number of blood cells was determined using a hemocytometer. Percentages of different cell types were determined using a Coulter LH 750 Hematology Analyzer (Beckman Coulter, Brea, CA, USA). As a result, absolute neutrophil, absolute lymphocyte, and absolute platelet counts were measured. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, the PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The median values of NLRs and PLRs before treatment and on day-PD were set as cut-off values, respectively.

Ethics statement. This study was conducted at the Osaka City University Graduate School of Medicine (Osaka, Japan), according to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines. The study protocol involved a retrospectively written research, pathological evaluation, and statistical analysis (18). The study complied with the provisions of the Declaration of Helsinki, and all patients provided written informed consent for their treatment and data collection. The study's retrospective protocol was approved by the ethics committee of Osaka City University (#926).

Statistical analysis. All statistical analyses were performed using the JMP software package (SAS, Tokyo, Japan). The relationship between factors was examined using the χ^2 test. The Kaplan–Meier method and the log-rank test were used for comparisons between PFS-ST and OS-CP. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. Multivariate analysis was performed using the Cox regression model. Statistical significance was defined as a *p*-value of less than 0.05.

Results

Clinicopathological features. Fifty-five patients with HRBC diagnosed as stage IIIB, IIIC, or IV who received ET as primary treatment were included in this study. Their clinicopathological features are shown in Table I. The median age was 65 (range=40-4) years old. The median tumor diameter was 41.0 mm (range=11.8-146.3 mm), with 41 patients (74.5%) having a skin infiltration. Only eight patients (14.5%) did not have lymph node metastasis and 22 patients (40.0%) had lymph node metastasis, which was diagnosed as N3. Forty patients (72.7%) had distant metastasis, with bone (24 cases; 43.6%) and lung (22 cases; 40.0%) being the most frequent metastatic sites, while 19 patients (34.5%) had distant metastases in multiple organs. From the above, 11 patients (20.0%) were diagnosed as stage IIIB, four (7.3%) as stage IIIC, and 40 (72.7%) as stage IV. All patients with bone metastasis received zoledronic acid or denosumab in combination with ET. Two patients (3.6%) received radiotherapy, one with brain metastasis and one with bone metastasis. All patients were positive for ER, but 13 patients (23.6%) were negative for PgR. Three patients (5.5%) were positive for HER2 but did not receive any HER2-targeted drugs such as trastuzumab. Ki67 was highly expressed in 25 patients (45.5%). Letrozole (LET) was the most commonly used primary endocrine therapy (35 cases; 63.7%). Thirty-seven patients (67.3%) were evaluated as responders in the ORR. Thirty patients (54.5%) who received primary ET were evaluated as PD because of an increase in the existing tumor, and 25 patients (45.5%) were evaluated as PD because of the appearance of new metastasis. The median PFS for first endocrine therapy was 406 days (range=10-2738 days). Forty-seven patients (85.5%) received another ET as second-line treatment. Sixteen patients (29.1%) died of breast cancer and one (1.8%) died of another cause.

Before treatment, the median NLR was 2.03 (range=0.66-10.66) and the median PLR was 132.10 (range=36.22-427.63). At day-PD, the median NLR was 1.72 (range=0.62-26.17) and the median PLR was 115.82 (range=49.84-

Table I. *Clinicopathological features of 55 patients with HRBC diagnosed as Stage IIIB, IIIC or IV who received ET as the primary treatment.*

Parameters (n=55)	Number of patients (%)
Age (years old)	65 (40-94)
Tumor size (mm)	41.0 (11.8-146.3)
Skin infiltration	
Negative/Positive	14 (25.5%)/41 (74.5%)
Lymph node metastasis	
N0/N1/N2/N3	8 (14.5%)/8 (14.5%)/17 (31.0%)/22 (40.0%)
The number of distant metastatic organs	
0/1/2/3	15 (27.3%)/21 (38.2%)/13 (23.6%)/5 (9.1%)/1 (1.8%)
Site of metastases	
Bone/Lung/Liver/Skin/Brain/Distant lymph node	24 (43.6%)/22 (40.0 %)/6 (10.9%)/1 (1.8%)/1 (1.8%)/12 (21.8%)
Stage	
3B/3C/4	11 (20.0%)/4 (7.3%)/40 (72.7%)
Estrogen receptor	
Negative/Positive	0 (0.0%)/55 (100.0%)
Progesterone receptor	
Negative/Positive	13 (23.6%)/42 (76.4%)
HER2	
Negative/Positive	52 (94.5%)/3 (5.5%)
Ki67	
Low/High	30 (54.5%)/25 (45.5%)
First ET	
LET/ANA/LH-RH agonist + TAM/EXE	35 (63.7%)/8 (14.5%)/8 (14.5%)/4 (7.3 %)
ORR	
Non-Responders/Responders	18 (32.7%)/37 (67.3 %)
NLR before treatment	2.03 (0.66-10.66)
PLR before treatment	132.10 (36.22-427.63)
NLR of cancer progression	1.72 (0.62-26.17)
PLR of cancer progression	115.82 (49.84-482.04)
Change of NLR during first endocrine therapy	
Decreased/Increased	33 (60.0%)/22 (40.0%)
Change of PLR during first endocrine therapy	
Decreased/Increased	33 (60.0%)/22 (40.0%)
Criteria for progression during first endocrine therapy	
Increased of existing tumor/Appearance of new metastasis	30 (54.5%)/25 (45.5%)
PFS for first endocrine therapy	406 (10-2738)

HRBC: Hormone receptor-positive breast cancer; ET: endocrine therapy. LET: Letrozole; ANA: anastrozole; LH-RH: luteinizing hormone-releasing hormone; TAM: tamoxifen; EXE: exemestane. HER2: Human epidermal growth factor receptor 2; ORR: objective response rate; NLR: neutrophil–to–lymphocyte ratio; PLR: platelets–to–lymphocyte ratio; PFS: progression-free survival.

482.04). In 33 patients (60.0%), NLR was decreased on day-PD compared with the day before treatment. The PLR also decreased in the same number of patients.

Correlations between clinicopathological features and the change in the NLR or PLR. Correlations between changes in NLR and PLR in patients receiving primary ET were examined (Table II). In the decreased PLR group, the tumor size was significantly larger (p=0.037). The decreased PLR group had significantly higher NLRs and PLRs before treatment (p=0.037, p=0.008, respectively). In the decreased NLR group, PLR declined significantly (p<0.001) on day-PD (p=0.021). In the increased PLR group, new metastases appeared more frequently (p=0.027). The PFS for first endocrine therapy was significantly longer in the group in which both NLR and PLR decreased (p=0.001 and p=0.037, respectively).

Association of NLR or PLR with prognosis. Kaplan–Meier survival curves for OS-CP and NLRs or PLRs are shown in Figure 1. An increased NLR was found to significantly contribute to a shorter OS-CP (p=0.040, log-rank) and similarly for an increased PLR (p=0.036, log-rank). In univariate analysis of OS-CP, an increased NLR or PLR was found to significantly contribute to a shorter OS-CP (Increased NLR; p=0.046, HR=2.656. Increased PLR; p=0.046, HR=2.697) (Table III). Furthermore, in multivariate analysis, an increased NLR was an independent factor, as was HER2-negative or the appearance of a new metastasis (p=0.035, HR=5.221).

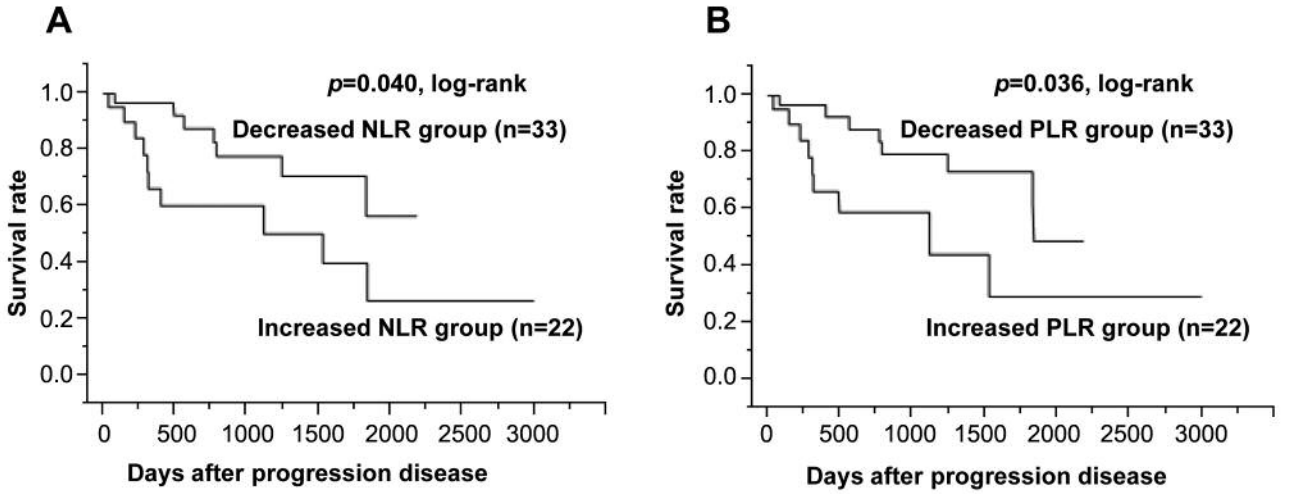

Figure 1. *Kaplan–Meier stratification curve for overall survival (OS) from the day on which the therapeutic effect of the primary endocrine therapy was evaluated as clinical progressive disease (cPD). (A) Change in neutrophil–lymphocyte ratio (NLR). (B) Platelet–lymphocyte ratio (PLR).*

Discussion

The immune microenvironment is profoundly involved in cancer progression and metastasis, and its monitoring and control influences the therapeutic effect and prognosis of chemotherapy and surgery. In recent years, the utility of tumor-infiltrating lymphocytes (TILs) that can be evaluated histopathologically has been reported to be an indicator of the immune microenvironment (19). However, the clinical use of TILs has not yet been established or applied to evaluating prognosis during the course of the disease. NLRs and PLRs are regarded as good indicators reflecting the balance between the tumor-promoting environment and the antitumor immune status, and they are relatively easy to evaluate over time. In this study, we evaluated the temporal changes in tumor immunity in patients receiving ET, which have never been reported.

Since both NLRs and PLRs are considered to be indicators of the state of immunity of the whole body, their correlation with prognosis was also observed in this study. However, NLRs and PLRs before treatment did not correlate with prognosis. This could be due to surgery that was performed on some of the stage IIIB or IIIC patients whose tumors had become smaller during ET. The fact that the ORR did not significantly differ in the prognosis supports this hypothesis.

Regarding PLR in breast cancer, a meta-analysis has reported that PLR was a more sensitive index in ER-positive and/or PgR-positive breast cancer than in ER- and PgR-negative breast cancer (2). The same meta-analysis has also reported that PLR correlated with the degree of progression, such as stage and lymph node metastasis2. PLR may be more susceptible to the patient's disease condition than NLR. Therefore, the tumor size and appearance of a new metastasis had influenced PLR. It has also been shown that in hepatocellular carcinoma (HCC), changes in PLR before and one month after hepatectomy affected prognosis (20). However, there have been no reports that have evaluated PLRs over time in breast cancer. In this study, increased PLRs had an impact on prognosis. PLR is also susceptible to the disease condition, and therefore it is an indicator of both the disease condition and tumor immunity.

Regarding NLR in breast cancer, it has been shown that it is correlated with cancer progression (21). However, a meta-analysis has shown that there was no involvement with clinical factors such as degree of progression on OS (1). If NLR was elevated at the time of recurrence in breast cancer, the prognosis was poor (22). Even in HCC, it has been reported that an increased NLR after resection or radiofrequency ablation was associated with a poor prognosis (23, 24). The group reported that the tumor was more likely to recur if a worsening of the anti-tumor immune response occurred after surgery. Furthermore, it has been demonstrated that changes in NLR were more important as indicators of prognosis than the preoperative or postoperative NLR (23, 24). In addition, we have also reported a reduction in TILs in patients with a postoperative recurrence who underwent preoperative chemotherapy (25). In summary, deterioration of tumor immunity is involved in recurrence after surgery, and NLR is an indicator reflecting only tumor immunity, unlike the PLR. Even in this study, increased NLRs were associated with poor prognosis after cancer progression. We hypothesized that both NLRs and PLRs would increase in association with cancer progression, but there were more cases with decreased NLRs or PLRs,

Table II. *Correlation between clinicopathological features and change of NLR or PLR during primary ET.*

Parameters	NLR during primary ET			PLR during primary ET		
	Decreased (n=33)	Increased (n=22)	*p*-Value	Decreased (n=33)	Increased (n=22)	*p*-Value
Age (years old)						
≤65	17 (51.5%)	11 (50.0%)		17 (51.5%)	11 (50.0%)	
>65	16 (48.5%)	11 (50.0%)	0.914	16 (48.5%)	11 (50.0%)	0.914
Tumor size (mm)						
≤41.0	14 (42.4%)	14 (63.6%)		13 (39.4%)	15 (68.2%)	
>41.0	19 (57.6%)	8 (36.4%)	0.128	20 (60.6%)	7 (31.8%)	0.037
Skin infiltration						
Negative	9 (27.3%)	5 (22.7%)		8 (24.2%)	6 (27.3%)	
Positive	24 (72.7%)	17 (77.3%)	0.711	25 (75.8%)	16 (72.7%)	0.805
Lymph node metastasis						
Negative	5 (15.2%)	3 (13.6%)		6 (18.2%)	2 (9.1%)	
Positive	28 (84.8%)	19 (86.4%)	0.879	27 (81.8%)	20 (90.9%)	0.358
Distant metastasis						
Negative	10 (30.3%)	5 (22.7%)		9 (27.3%)	6 (27.3%)	
Positive	23 (69.7%)	17 (77.3%)	0.545	24 (72.7%)	16 (72.7%)	1.000
Progesterone receptor						
Negative	8 (24.2%)	5 (22.7%)		7 (21.2%)	6 (27.3%)	
Positive	25 (75.8%)	17 (77.3%)	0.899	26 (78.8%)	16 (72.7%)	0.612
HER2						
Negative	32 (97.0%)	20 (90.9%)		32 (97.0%)	20 (90.9%)	
Positive	1 (3.0%)	2 (9.1%)	0.341	1 (3.0%)	2 (9.1%)	0.341
Ki67						
Low	19 (57.6%)	11 (50.0%)		20 (60.6%)	10 (45.5%)	
High	14 (42.4%)	11 (50.0%)	0.589	13 (39.4%)	12 (54.5%)	0.277
ORR						
Non-responders	8 (24.2%)	10 (45.5%)		9 (27.3%)	9 (40.9%)	
Responders	25 (75.8%)	12 (54.5%)	0.300	24 (72.7%)	13 (59.1%)	0.300
NLR before treatment						
Low	15 (45.5%)	13 (59.1%)		13 (39.4%)	15 (68.2%)	
High	18 (54.5%)	9 (40.9%)	0.331	20 (60.6%)	7 (31.8%)	0.037
PLR before treatment						
Low	14 (42.4%)	14 (63.6%)		12 (36.4%)	16 (72.7%)	
High	19 (57.6%)	8 (36.4%)	0.128	21 (63.6%)	6 (27.3%)	0.008
NLR of cancer progression						
Low	20 (60.6%)	8 (36.4%)		17 (51.5%)	11 (50.0%)	
High	13 (39.4%)	14 (63.6%)	0.081	16 (48.5%)	11 (50.0%)	0.914
PLR of cancer progression						
Low	21 (63.6%)	7 (31.8%)		19 (57.6%)	9 (40.9%)	
High	12 (36.4%)	15 (68.2%)	0.021	14 (42.4%)	13 (59.1%)	0.234
Change of NLR during first ET						
Decreased	-	-		29 (87.9%)	4 (18.2%)	
Increased	-	-	-	4 (12.1%)	18 (81.8%)	<0.001
Change of PLR during first ET						
Decreased	29 (87.9%)	4 (18.2%)		-	-	
Increased	4 (12.1%)	18 (81.8%)	<0.001	-	-	-
Criteria for progression during first ET						
Increased of existing tumor	19 (57.6%)	11 (50.0%)		22 (66.7%)	8 (36.4%)	
Appearance of new metastasis	14 (42.4%)	11 (50.0%)	0.589	11 (33.3%)	14 (63.6%)	0.027
PFS for first ET						
Short	11 (33.3%)	17 (77.3%)		13 (39.4%)	15 (68.2%)	
Long	22 (66.7%)	5 (22.7%)	0.001	20 (60.6%)	7 (31.8%)	0.037

NLR: Neutrophil–to–lymphocyte ratio; PLR: platelets–to–lymphocyte ratio; HER2: human epidermal growth factor receptor 2; ORR: objective response rate. ET: endocrine therapy; PFS: progression-free survival.

Table III. *Univariate and multivariate analysis with respect to overall survival after cancer progression.*

Parameters	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Age at treatment						
≤65 *vs.* >65	0.755	0.273-1.978	0.568			
Tumor size						
≤41.0 *vs.* >41.0	1.169	0.445-3.128	0.749			
Skin infiltration						
Negative/Positive	1.524	0.491-6.665	0.493			
Lymph node metastasis						
Negative *vs.* Positive	3.634	0.738-65.664	0.129			
Distant metastasis						
Negative *vs.* Positive	1.184	0.417-4.219	0.765			
Progesterone receptor						
Negative *vs.* Positive	1.530	0.497-6.652	0.486			
HER2						
Negative *vs.* Positive	-	-	0.019	-	-	0.002
Ki67						
Negative *vs.* Positive	0.815	0.294-2.132	0.677			
ORR						
Non-Responders *vs.* Responders	0.384	0.145-1.075	0.067	0.484	0.166-1.445	0.188
NLR of cancer progression						
Low *vs.* High	1.368	0.525-3.772	0.522			
PLR of cancer progression						
Low *vs.* High	1.525	0.585-4.205	0.389			
Change of NLR during first ET						
Decreased *vs.* Increased	2.656	1.017-7.337	0.046	5.221	1.116-29.777	0.035
Change of PLR during first ET						
Decreased *vs.* Increased	2.697	1.020-7.260	0.046	1.312	0.241-6.760	0.748
Criteria for progression during first ET						
Increased of existing tumor *vs.* Appearance of new metastasis	4.137	1.526-13.059	0.005	7.269	2.195-29.960	0.001
PFS for first ET						
Short *vs.* Long	0.522	0.179-1.384	0.194			

CI: Confidence intervals; HER2: human epidermal growth factor receptor 2; ORR: objective response rate; NLR: neutrophil–to–lymphocyte ratio; PLR: platelets–to–lymphocyte ratio; ET: endocrine therapy; PFS: progression-free survival.

although not statistically significant, than cases with increased NLRs or PLRs. The antitumor immune response may be different between postoperative recurrence and cancer progression.

Using univariate analysis, OS-CP was correlated with HER2-negative, increased NLR, a change in PLR, and the appearance of a new metastasis. Multivariate analysis showed that HER2-negative, increased NLR, and the appearance of a new metastasis were independent prognostic factors. It has also been previously reported that the appearance of a new metastasis was a poor prognostic factor (26). In recent years, new HER2-targeted drugs have been clinically used, allowing for prolongation of prognosis. We hypothesized that the use of a regimen that includes a combination of HER2-targeted drugs in later treatment affects the prognosis in HER2-positive patients. An increased NLR, which is an indicator of worsening tumor immunity, was thought to influence subsequent prognosis.

This study had some limitations. The number of cases studied was small, and the selection of treatment after the second-line therapy was different. Of all patients, 85.5% choose ET as their second-line treatment, but for some, chemotherapy was selected as the second-line treatment. Currently, CDK 4/6 inhibitors are being used clinically as a treatment for patients who respond poorly to ET. The treatment strategy for advanced HRBC is evolving. However, evaluating changes in NLR and PLR is a method that can be performed relatively easily in the clinic, making it a potentially valuable technique.

Conclusion

In conclusion, changes in NLR and PLR, when the therapeutic effect of ET is poor, become prognostic indicators. An increase in ratios would suggest that the disease has advanced, and it would suggest introduction of

chemotherapy or a CDK 4/6 inhibitor early or careful follow-up during subsequent endocrine therapy.

Conflicts of Interest

The Authors have no conflicts of interest to disclose regarding this study.

Authors' Contributions

All Authors were involved in the preparation of this manuscript. KoT collected the data and wrote the manuscript. SK, YA, WG, KaT, MS, RA, and TT performed the operation and designed the study. KoT, SK, and ST summarized the data and revised the manuscript. KH and MO provided a substantial contribution to the study design, performed the operation, and revised the manuscript. All Authors read and approved the final manuscript.

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