ORIGINAL ARTICLE

Basic and combined peripheral biomarkers have no predictive and prognostic value in breast cancer patients undergoing pre-operative systemic therapy

Los biomarcadores periféricos básicos y combinados no tienen valor predictivo ni pronóstico en pacientes con cáncer de mama sometidas a terapia sistémica preoperatoria

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Abstract

Objective: *The main goal in breast cancer patients receiving neoadjuvant chemotherapy (NAC) is to achieve a pathologic complete response (pCR). Our study examines whether neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), NLR/PLR, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation-value (PIV) indices can be used to determine pCR and prognosis.* **Methods:** *The study included 228 patients who received NAC for breast cancer between 2010 and 2021.* **Results:** *Fifty-nine (25.9%) patients had pCR to NAC. In univariate analysis, a significant difference was found between clinical node status, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), breast cancer molecular subtypes, and pCR ($p < 0.05$). However, in multivariate analysis, only breast cancer molecular subtypes and HER2 status were significantly associated with pCR ($p < 0.05$).* **Conclusions:** *Our study did not find a significant relationship between NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices and pCR, disease-free survival, and overall survival in breast cancer patients who received NAC.*

Keywords: *Neoadjuvant chemotherapy. Breast cancer. Disease-free survival.*

Resumen

Objetivo: *El propósito principal en las pacientes con cáncer de mama que reciben quimioterapia neoadyuvante (NAC) es lograr una respuesta patológica completa (RPC). Nuestro estudio examina si el índice neutrófilos/linfocitos (INL), el índice plaquetas/linfocitos (IPL), el índice monocitos/linfocitos (IML), la ratio INL/IPL, el índice de inmunidad-inflamación sistémica (IIS), el índice de respuesta inflamatoria sistémica (IRIS) y el valor de pan-inmuno inflamación (VPI) pueden utilizarse para determinar la RPC y el pronóstico.* **Métodos:** *El estudio incluyó 228 pacientes que recibieron NAC por cáncer de mama entre 2010 y 2021.* **Resultados:** *Cincuenta y nueve (25.9%) pacientes tuvieron RPC a NAC. En el análisis univariante, se encontró una diferencia significativa entre el estado de los ganglios clínicos, el receptor de estrógenos, el receptor de progesterona, el receptor del factor de crecimiento epidérmico humano 2 (HER2), los subtipos moleculares de cáncer de mama y la RPC ($p < 0,05$). Sin embargo, en el análisis multivariante solo los subtipos moleculares de cáncer de mama y el estado de HER2*

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se asociaron significativamente con la RPC (p < 0.05). **Conclusiones:** *Nuestro estudio no encontró una relación significativa del INL, el IPL, el IML, la INL/IPL, el IIS, el IRIS y el VPI con la RPC, la supervivencia libre de enfermedad y la supervivencia global en pacientes con cáncer de mama que recibieron NAC.*

Palabras clave: *Quimioterapia neoadyuvante. Cáncer de mama. Supervivencia libre de enfermedad.*

Introduction

Breast cancer surpassed lung cancer as the most common cause of cancer globally in 2020. In addition, breast cancer still accounts for a significant proportion of cancer-related deaths among women[1]. Therefore, focusing on the treatment of patients with breast cancer is critical for public health.

In recent years, neoadjuvant chemotherapy (NAC) has been used with increasing frequency in breast cancer. However, there are uncertainties about which patients are sensitive to NAC and which patients are not sensitive to NAC and, therefore, delayed surgical treatment. Hence, it is essential to determine who will benefit from NAC to optimize the treatment of patients. Estrogen receptor (ER), progesterone receptor (PR), Ki67 level, and human epidermal growth factor receptor 2 (HER2) status are often used to predict response to NAC. However, they do not accurately predict pathologic complete response (pCR). Tumor-infiltrating lymphocytes (TILs), programmed death-ligand 1 expression, artificial intelligence-assisted magnetic resonance imaging, quantitative ultrasound, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography can also be used. However, these examinations are costly. In addition, access to these examinations is only sometimes possible, and further studies are needed for their use in routine practice[2]. Therefore, there is a need for parameters that are inexpensive, easily accessible, and not difficult to interpret[3]. For this purpose, the literature has turned toward inflammatory bioindices analyzed from peripheral blood. These indices are calculated by various ratios of white blood cell (W), neutrophil (N), monocyte (M), platelet (P), and lymphocyte (L) cells in peripheral blood. The literature has mainly focused on the association of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) with pCR and survival. However, studies have shown that NLR and PLR have conflicting results in predicting pCR, disease-free survival (DFS), and overall survival (OS)[4-8]. However, few studies have focused on more combined peripheral indices such as NLR/PLR, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation-value (PIV). These studies suggest that more complex calculations predict PCR and prognosis better than individual biomarkers[7]. However, there are few publications on combined indices and conflicting reports on these indices.

The main goal of breast cancer patients receiving NAC is to achieve a PCR. In the above-mentioned studies, the main issue investigated is whether peripheral biomarkers can predict pCR in breast cancer patients receiving NAC. However, giving NAC to breast cancer patients to achieve an axillary complete response based on these indices may lead to overtreatment of the axilla because axillary dissection (AD) is recommended even if the patient's axilla remains clinically positive after NAC or if micrometastases are detected on sentinel lymph node biopsy (SLNB) in patients whose axilla turns clinically negative. However, AD is not always recommended in patients who have not received NAC if the axilla is positive under certain conditions or if macrometastasis is detected on SLNB[9].

For the reasons mentioned above, we focused on the contradictions and problems in the clinical use of simply calculated indices such as NLR, PLR, monocyte lymphocyte ratio (MLR), and more combined indices such as NLR/PLR, SII, SIRI, and PIV. We aimed to examine the relationship of these indices with pCR, DFS, and OS in a group of breast cancer patients receiving NAC. Our study is also important as it is the first publication in the literature to evaluate these indices together in terms of both pCR and prognosis.

Methods

Patients

Patients who were admitted to SBU Izmir Tepecik Training and Research Hospital between 2010 and 2021 and received NAC for breast cancer were included in the study. After obtaining permission from the Local Ethics Committee, patient data were obtained retrospectively from the electronic record system and physical files of the medical oncology department.

All patients were diagnosed histopathologically and were presented to the multidisciplinary session after appropriate screening according to their stage. The standard treatment regimens for patients with NAC decisions are anthracycline and taxane-based. Patients with HER2-positive tumors received standard trastuzumab in addition to anthracycline and taxane.

Surgical procedures included breast conserving surgery, level 1, 2, and 3 oncoplastic surgery or mastectomy. The axilla was evaluated by imaging and physical examination after NAC. SLNB was performed in patients with clinically negative axilla after NAC. No additional procedure was performed in patients with negative SLNB, while AD was performed in patients with positive (macro- or micrometastases). Clinical and pathological tumors were defined according to the American Joint Committee Cancer Staging Manual 8th Edition.

Exclusion criteria were as follows: diagnosis of cancer in an organ other than breast cancer, active infection at the time of diagnosis, inflammatory or autoimmune disease, recent steroid therapy, inflammatory breast cancer, metastasis to distant organs at the time of diagnosis, no surgery after NAC, and no follow-up.

Pathological assessments

Residual cancer burden (RCB) was calculated by the computerized MD Anderson RCB Calculator[10]. Accordingly, RCB 0 = pCR. pCR was defined as the absence of a tumor in both breast and axillary lymph nodes (LNs) after NAC (ypT0/ypTis, ypN0). The non-pCR group included RCBs 1, 2, and 3 (minimal, moderate, and extensive residual disease, respectively).

Study patients were classified into four main molecular subtypes. HR-positivity (HR+) was defined as ER-positive and/or PR-positive, while HR-negativity (HR–) was defined as ER-negative and PR-negative. HER2-positivity (HER2+) was defined as a score of 3 + on immunohistochemical staining and/or positive *HER2* gene amplification by FISH. Triple-negative breast cancer was defined as HR–/HER2-, HER2-enriched breast cancer as HR–/HER2+, luminal A as HR+, HER2–, Ki67 ≤ 14 and luminal B as HR+, HER2–, Ki67 > 14 or HR+, and HER2+[11].

Blood sample analysis

NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV values were calculated from peripheral blood values obtained from patients diagnosed with breast cancer before NAC treatment. The indices were calculated as follows; NLR; N/L, PLR; P/L, MLR; M/L, SII; N*P/L, SIRI; N*M/L, PIV; and N*P*M/L.

Patient follow-up and prognostic assessment

The patients whose treatments were completed were followed up in outpatient departments. Patients were followed up by physical examination, blood tests, and imaging methods and additional procedures were performed when necessary.

Statistical analysis

Statistical analyses were performed using IBM® Statistical Package for the Social Sciences (SPSS)® 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) software. The conformity of the variables to normal distribution was analyzed using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were given as mean ± standard deviation for normally distributed variables, median and min-max for those not normally distributed. Descriptive statistics of categorical variables obtained from sociodemographic and clinical information were analyzed using frequency and percentage values. Pearson's or Fisher's Exact X^2 test was used to examine the characteristics of patients between pCR response states. With receiver operative characteristics (ROC) analysis, cutoff values were determined for NLR, MLR, PLR, PIV, SII, and SIRI parameters (follow-up parameters analyzed) according to pCR status. According to these cutoff values, dichotomous (Low/High) variables were created for each parameter. Univariate and multivariate logistic regression analyses were performed to evaluate the effects of the characteristic variables of the disease and the follow-up parameters on the pCR response. Cox regression survival analysis was performed on these follow-up parameters (NLR, PLR, NLR/PLR, MLR, SIRI, SII, and PIV) to examine whether they could be predictive markers on OS and DFS times and whether a model could be established. Kaplan–Meier survival analysis was performed to compare OS and DFS durations between dichotomous (Low/High) variables of NLR, PLR, NLR/PLR, MLR, SIRI, SII, and PIV parameters. P values below 0.05 were considered statistically significant.

Table 1. Clinicopathological characteristics of the patients

Characteristics	n	%
Age		
Median (range)	50 (24-78)	
Clinical T stage		
1	31	13.6
2	150	65.8
3	31	13.6
4	16	7.0
Clinical T stage groups		
T1-T2	181	79.4
T3-T4	47	20.6
Clinical node stage		
0	46	20.2
1	137	60.1
2	41	18.0
3	4	1.8
Clinical node status		
Negative	46	20.2
Positive	182	79.8
Stage		
1	3	1.3
2	147	64.5
3	78	34.2
Stage groups		
≤ 2	150	65.8
3	78	34.2
Grade		
Missing	3	1.3
Good	5	2.2
Moderate	126	55.3
Poor	94	41.2
Moleculer subtype		
Luminal A	24	10.5
Luminal B	123	53.9
ER and PR–. Her2+	34	14.9
Triple-negative	47	20.6
Histotype		
Invasive ductal carcinoma	206	90.4
Other histology types	22	9.6
Estrogen receptor status		
Negative	81	35.6
Positive	147	64.4
PR receptor status		
Negative	83	36.4
Positive	145	63.6
HER-2 status		
Negative	162	71.1
Positive	66	28.9
Ki-67 index, n (%)		
Median (range)	30 (0-90)	
Ki67 classification		
Ki67 < 14	34	14.9
Ki67 ≥ 14	194	85.1
Pathologic complete response		
Yes	59	25.9
No	169	74.1
Recurrence		
No	188	82.5
Yes	40	17.5
Recurrence location		
No	188	82.5
Liver	5	2.2
Bone	3	1.3
Lung	6	2.6
Brain	4	1.8
Multiple	16	7.0
Breast axilla	6	2.6
Mortality		
Ex	43	18.9
Live	185	81.1

HER2: human epidermal growth factor receptor 2.

Results

The study included 228 patients with breast cancer who received NAC. The median age of the patients was 50 years (range 24-78). Fifty-nine (25.9%) patients had pCR to NAC and 169 (74.1%) patients had non-pCR. Recurrence was detected in 40 (17.5%) patients. Forty-three (18.9%) of the patients died. Detailed clinicopathological characteristics of the patients are summarized in table 1.

The relationship between pathological complete response and indices was calculated according to ROC analysis. Cutoff values of NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices were calculated according to maximum specificity and sensitivity. According to this analysis, no significant difference was found between pCR and indices ($p > 0.05$) (Table 2).

The relationship between pCR and clinicopathological characteristics of the patients was examined by univariate and multivariate analyses. In univariate analysis, a significant difference was found between clinical node status, ER, PR, HER-2, breast cancer molecular subtypes, and pCR ($p < 0.05$). However, in multivariate analysis, only breast cancer molecular subtypes and HER-2 status were significantly associated with pCR ($p < 0.05$). Detailed data are given in table 3.

Cox regression analysis was applied to examine whether NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV

Table 2. ROC curve analyses for pathological complete response

Test result variable (s)	AUC	Standard error	p	95% CI for AUC		Sensitivity (%)	Specificity (%)	Cut-off value
				Lower bound	Upper bound			
MLR	0.581	0.044	0.067	0.494	0.668	55.2	56.4	0.262
NLR	0.566	0.045	0.138	0.477	0.654	55.2	55.8	2.24
PIV	0.557	0.045	0.198	0.468	0.646	55.2	56.4	335.7
PLR	0.500	0.047	0.998	0.407	0.593	50.0	57.0	141.2
SII	0.540	0.046	0.362	0.450	0.630	50.0	64.2	597.5
SIRI	0.584	0.044	0.057	0.498	0.669	53.4	57.6	1.18

The test result variable (s): NLR, MLR, PLR, SII, and SIRI have at least one tie between the positive actual state group and the negative actual state group. $p < 0.05$ considered significant. Youden's J statistic used for cutoff. AUC: area under curve; CI: confidence interval; ROC: receiver operating characteristic; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PIV: pan-immune-inflammation-value; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index, SIRI: systemic inflammation response index.

Table 3. Univariate and multivariate logistic regression analysis for the predictors of pathological complete response

Factors	Univariate analysis				Multivariate analysis			
	OR	95% C.I. for EXP (B)		p	OR	95% C.I. for EXP (B)		p
		Lower	Upper			Lower	Upper	
Age	1.0	1.0	1.1	0.142				
Clinical T stage (T1-2 vs. T3-4)	1.2	0.6	2.5	0.664				
Clinical node status (Positive vs. Negative)	2.8	1.4	5.6	0.003	2.1	0.8	4.5	0.057
Triple-negative versus luminal A	17.0	2.1	136.9	0.008	30.8	2.5	380.9	0.008
Triple-negative versus luminal B	3.8	1.8	8.1	< 0.0001	14.8	2.8	79.5	0.002
Triple-negative versus ER and PR–. HER2+	1.6	0.6	3.7	0.356	4.1	1.1	16.0	0.040
Stage (≤ 2 vs. 3)	1.2	0.7	2.2	0.563				
Histopathology (IDC vs. Other)	1.9	0.8	4.9	0.172				
ER (Positive vs. Negative)	4.1	2.2	7.6	< 0.0001	2.9	0.4	24.0	0.325
PR (Positive vs. Negative)	3.7	2.0	6.9	< 0.0001	1.4	0.2	7.6	0.737
HER-2 status (Negative vs. Positive)	3.8	2.0	7.2	< 0.0001	6.1	2.2	16.9	< 0.0001
Ki67 index (High vs. Low)	1.2	0.5	2.7	0.735				
MLR group (High vs. Low)	1.6	0.9	2.9	0.131				
NLR group (High vs. Low)	1.5	0.8	2.7	0.193				
PIV group (High vs. Low)	1.5	0.8	2.6	0.221				
PLR group (High vs. Low)	1.3	0.7	2.3	0.429				
SII group (High vs. Low)	1.8	1.0	3.3	0.055				
SIRI group (High vs. Low)	1.6	0.9	2.3	0.140				

Logistic regression analysis was used and $p < 0.05$ considered significant.
CI: confidence interval; OR: odds ratio; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PIV: pan-immune-inflammation-value; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index, SIRI: systemic inflammation response index.

Table 4. Univariate and multivariate Cox regression analysis for OS and DFS

Variables	Univariate analysis						Multivariate analysis					
	β	SE	p	OR	95.0% CI for OR		β	SE	p	OR	95.0% CI for OR	
					Lower	Upper					Lower	Upper
OS												
MLR	–0.18	0.14	0.177	0.83	0.64	1.09	–0.23	0.18	0.200	0.80	0.56	1.13
NLR	–0.09	0.13	0.518	0.92	0.71	1.19	–0.23	0.19	0.224	0.79	0.55	1.15
PIV	0.04	0.13	0.783	1.04	0.80	1.35	0.09	0.23	0.700	1.09	0.70	1.71
PLR	–0.10	0.13	0.468	0.91	0.70	1.18	–0.14	0.18	0.435	0.87	0.60	1.24
SII	0.12	0.14	0.401	1.12	0.86	1.47	0.35	0.21	0.095	1.42	0.94	2.16
SIRI	–0.05	0.13	0.725	0.95	0.73	1.24	0.05	0.24	0.828	1.05	0.66	1.68
DFS												
NLR	–0.187	0.135	0.168	0.830	0.636	1.082	–0.189	0.174	0.276	0.828	0.589	1.163
MLR	–0.051	0.134	0.705	0.951	0.732	1.235	–0.174	0.191	0.363	0.840	0.578	1.222
PLR	0.047	0.134	0.728	1.048	0.806	1.363	0.366	0.253	0.148	1.441	0.878	2.365
PIV	–0.077	0.134	0.567	0.926	0.712	1.205	–0.094	0.186	0.613	0.910	0.633	1.310
SII	0.148	0.138	0.282	1.159	0.885	1.519	0.343	0.210	0.102	1.409	0.934	2.126
SIRI	–0.119	0.134	0.375	0.888	0.682	1.155	–0.337	0.255	0.188	0.714	0.433	1.178

Cox Regression analysis was used and $p < 0.05$ considered significant. CI: confidence interval; SE: standard error; DFS: disease-free survival; OS: overall survival; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PIV: pan-immune-inflammation-value; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; OR: odds radio.

indices could be used in univariate and multivariate calculations for OS and DFS follow-up. It was determined that each index could not be used in the follow-up of OS and DFS in the analyses performed alone or in combination ($p > 0.05$). Detailed data are given in table 4.

The low and high groups created in NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices separately in pCR and non-pCR groups were evaluated in terms of OS, and DFS evaluation. However, no significant discrimination was found in the mentioned indices ($p > 0.05$). Detailed representation is available in figuras 1 and 2.

Discussion

Our study evaluated NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices regarding pCR, DFS, and OS in breast cancer patients receiving NAC. In our study, these indices failed to predict pCR, DFS and OS. This finding is critical because our study underlines that the parameters mentioned above are still contradictory in deciding NAC in clinical use. As far as we can see, none of the publications on this subject have analyzed both pCR and prognosis together using the above-mentioned indices simultaneously.

As a result of tumor-induced changes in the immune system, inflammatory immune cells in the peripheral blood may be affected[12]. Lymphocytes in peripheral blood are related to adaptive immunity. In addition, lymphocytes may show anti-tumoral activity by inhibiting tumor growth and progression. Platelets play an essential role in the development and spread of cancer and in regulating inflammation. Neutrophils have a central role in the systemic inflammatory response and immunity. Neutrophils can also initiate metastasis in breast cancer by secreting immunosuppressive mediators and angiogenetic factors. Monocytes are also associated with tumor angiogenesis and metastasis[2,13]. Theoretically, it can be said that each of the mentioned indices or their combinations may be related to pCR, DFS, and OS in breast cancer patients. In the literature, an increasing number of publications have examined the relationship between these indices and breast cancer patients who will receive NAC. Among these indices, NLR and PLR indices have been analyzed most frequently for this purpose. However, studies have shown that NLR and PLR have conflicting results in predicting pCR, DFS and OS in breast cancer patients receiving NAC[4-8]. With the idea that more combined indices may be better predictors, Graziano et al.[6] compared NLR and PLR values with NLR/PLR combination. This study found that NLR and PLR alone could not predict pCR, whereas there was a significant relationship between NLR/PLR combination and pCR. In two other studies in the literature, it was shown that NLR and PLR values were better in indicating pCR when evaluated in combination rather than when used alone[3,14]. In these three studies, NLR/PLR combination was found to be significant in

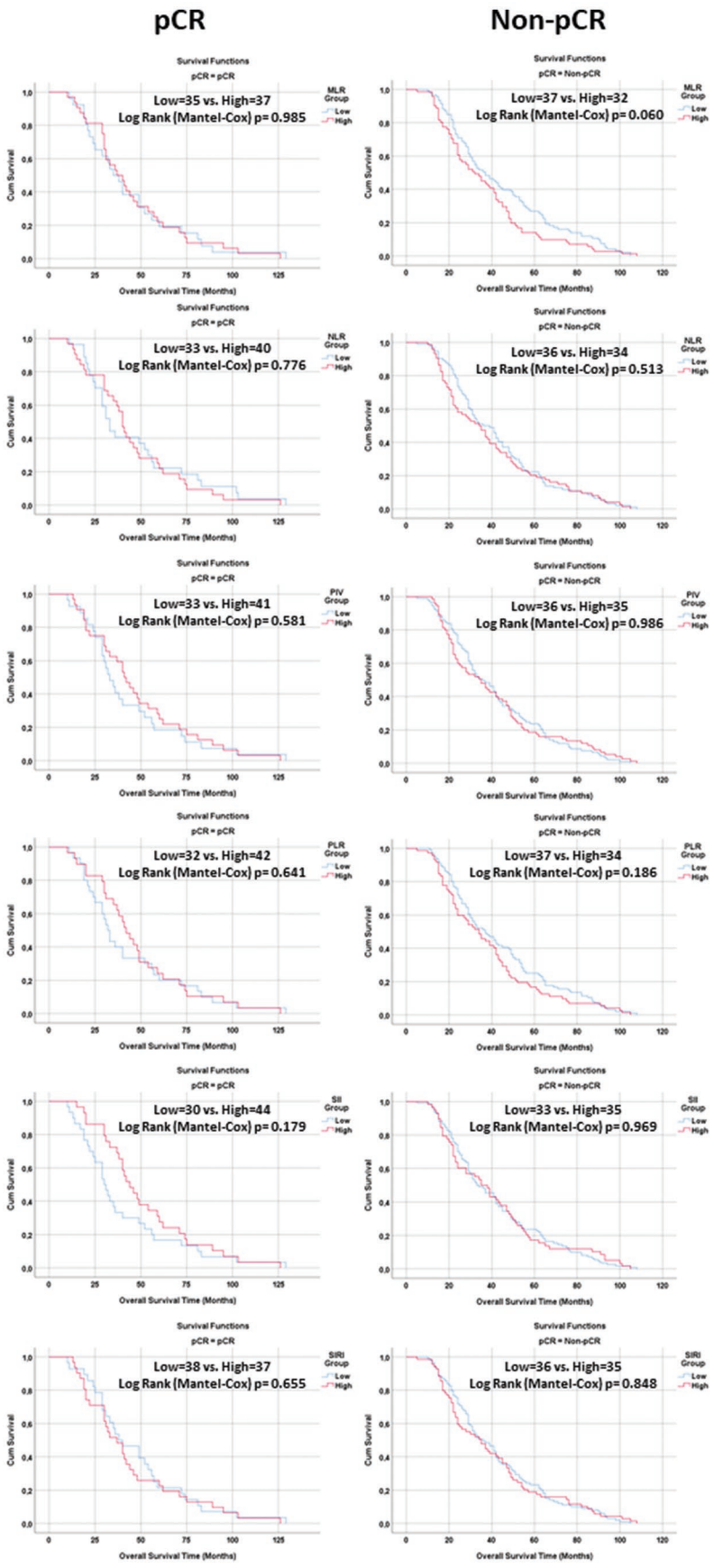

Figure 1. *Comparison of low and high overall survival times in rates and indices in pathologic complete response (pCR) and non-pCR groups.*

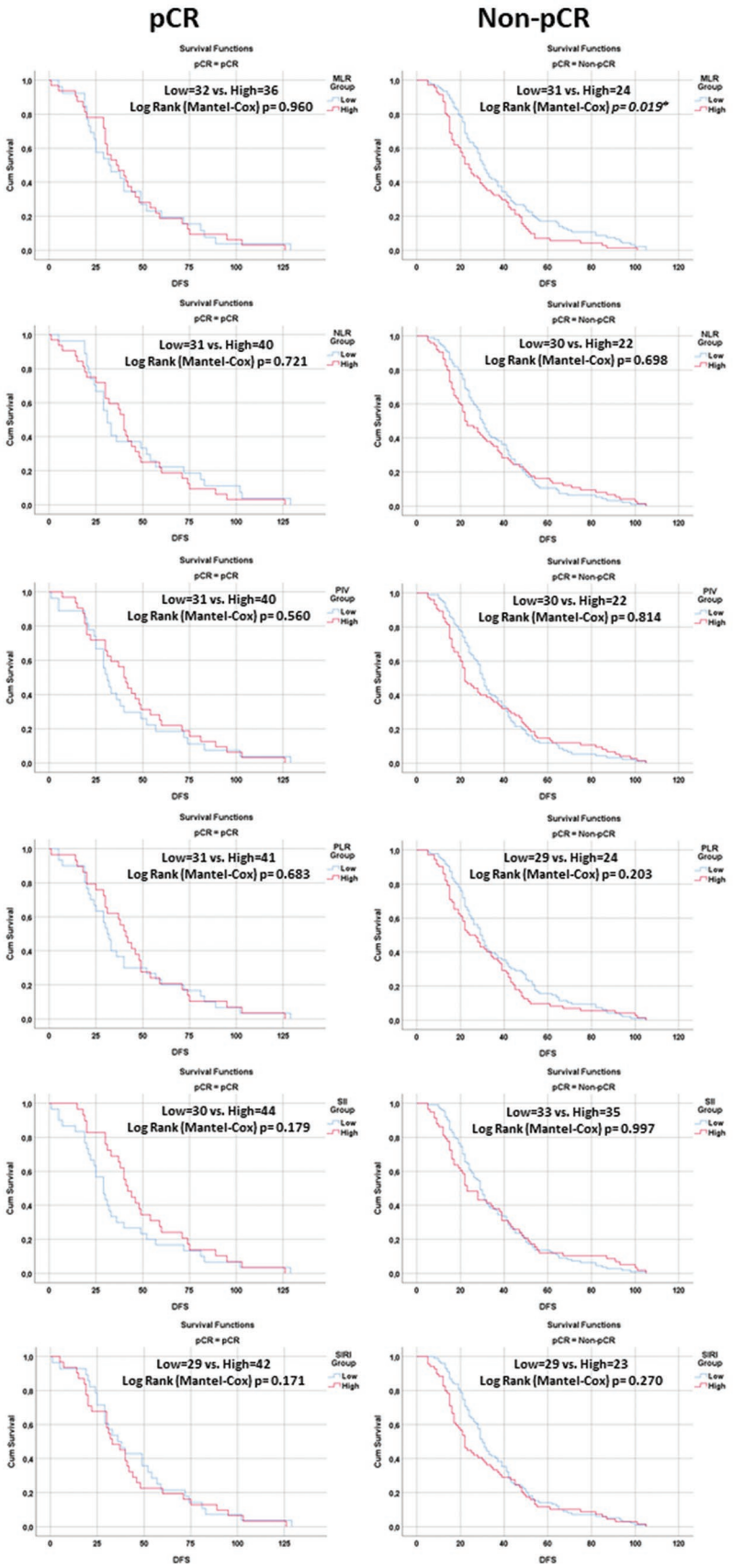

Figure 2. *Comparison of low and high disease-free survival times in rates and indices in pathologic complete response (pCR) and non-pCR groups.*

evaluating pCR in contrast to our study. Among these three studies, only Kim et al.[3] analyzed the relationship between prognosis and NLR/PLR combination and found a significant relationship in contrast to our study. However, there is a significant methodological difference between the study of Kim et al.[3] and our study regarding pCR evaluation, as we will mention later. In addition, there are not enough publications on NLR/PLR index in the literature yet. As far as we can see, our article is the first study in the English literature showing that the NLR/PLR combination fails to predict pCR and prognosis.

One of the other combined parameters is SIRI. In SIRI calculation, monocytes are included in the calculation in addition to NLR. First, Dong et al.[15] analyzed the relationship between SIRI, and pCR. According to this study, SIRI showed pCR to NAC better than other indices (lymphocyte monocyte ratio, absolute lymphocyte count, and NLR). However, this study did not analyze DFS and OS. In the study of Chen et al.[13], SIRI was significant in determining OS and DFS in breast cancer patients receiving NAC. However, no significant difference was found in terms of pCR, similar to our study.

In SII, another combined parameter, platelets, which have an essential role in the development and spread of breast cancer, are included in the calculation in addition to NLR. In the study of Yang et al.[16], a significant correlation was found between NLR, PLR, SII, and pCR. In contrast, in another study of Chen et al.[17], no significant correlation was found between SII and pCR as in our study. However, Chen et al.[17] found that patients with low SII values had longer DFS and OS rates.

Compared with individual blood cell parameters, combined indices may more comprehensively identify multiple components of antitumor immunity, each of which may reflect and regulate different aspects of antitumor immunity. For this purpose, in the study of Şahin et al.[7], the PIV index, which includes all the parameters mentioned above (neutrophils, platelets, monocytes, and lymphocytes), was used. Indeed, supporting the theoretical knowledge, NLR, PLR, MLR, and PIV successfully showed pCR in univariate analysis. In contrast, only PIV, a more complex marker, maintained its statistical value in multivariate analysis. Furthermore, PIV was found to have a prognostic effect on survival. This is important because it is the first study in the literature to examine the relationship between PIV value and response to NAC and survival in breast cancer. However, contrary to this study, we could not reach similar results in our study.

When considered together with our study, many factors can be counted to explain the contradictory results of those mentioned above simple and complex indices on pCR and prognosis in breast cancer patients receiving NAC. Many factors can easily affect inflammatory markers (lymphocytes, neutrophils, platelets, and monocytes). For example, many factors can easily affect inflammatory events, including connective tissue diseases, medications used, bacterial or viral diseases, nutritional status, severe stress, and severe exercise[3]. In addition, breast cancers have the least immunogenic type compared to other cancer types[2]. In addition, TILs are less common in HR+ positive breast cancers compared to HR– breast cancers[18]. In other words, anticancer immunity is not dominant in hormone receptor-positive breast cancers. Therefore, it is thought that absolute lymph count is not a good predictor in HR+ breast cancers compared to HR– breast cancers[19]. Lymphocyte count is included in the denominator of calculations in all indices we investigated and, therefore, affects all calculations. Finally, it is thought that lymphocytic infiltration in the tumor microenvironment is not sufficiently reflected in peripheral blood cells[20]. All the factors mentioned above give us a clue to explain the conflicting data on these indices.

One of the reasons for the conflicting reports on these indices is the methodological difference between studies. There are differences in the definition of pCR in the literature. Miller-Payne (MP) classification was used in some publications. In this classification, unlike the RCB classification, the axilla is not evaluated, and only the response in the breast is considered. In other words, a patient with a complete response to the tumor in the breast is considered to have a complete response even if tumors are detected in the LNs. In addition, in some of the studies using the MP classification, both MP 4 (> 90% response to NAC) and MP 5 (no tumor cells) were included in the group of patients who responded to NAC. However, it is known that the survival time of patients with pCR is higher than those with residual cancer[21]. For example, in the studies of Kim et al.[3] evaluating NLR/PLR combination and in two separate studies of Chen et al. evaluating SIRI[13] and SII[17], clinical response was evaluated as MP 4-5. In contrast to these studies, RCB was used in two other studies evaluating NLR/PLR combination[6,14], SIRI by Dong et al.[15], NLR, PLR, and SII by Yang et al.[16], and PIV index by Şahin et al.[7]. This

confusion in the evaluation of pathological response may have caused contradictions in the correct evaluation of the indices. However, to use a standard criterion in the literature and make comparisons, it would be more accurate to use RCB when investigating pCR as in our study[22].

Although there are publications examining the relationship of these indices with pCR and prognosis, there are very few comments on how their clinical use will be in routine practice. Therefore, we would like to discuss a topic that has not been emphasized in the literature. In the recently updated NCCN guidelines, patients with clinically node negative or clinically non-palpable lymph but with up to two positive LNs by imaging or biopsy may undergo SLNB if NAC was not performed. However, in breast cancer patients who receive NAC, AD is performed if there is a clinically positive LN after NAC or a positive sentinel LN (micro or macrometastasis)[9]. In this case, in patients with low axillary LN metastasis in whom NAC is not considered (especially in HR+, HER2– tumors), giving NAC by relying on the indices listed above may lead to some problems. The most important of these problems will arise if the patient's axilla does not respond fully to NAC. A patient with a low axillary tumor burden who would not usually be given NAC can typically be satisfied with SLNB. In contrast, AD will be necessary in the patient receiving NAC, even if micrometastases are found on SLNB. In this case, overtreatment will be applied to the patient's axilla. In addition, since the methods used to reduce false negativity during SLNB application in the patient receiving NAC are technically more complex, we argue that the decision of NAC in patients with breast cancer should not be based on the mentioned indices.

Our study has limitations: a small number of patients, single-center experience, and retrospective nature.

Conclusion

Our study did not find a significant relationship between NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices and pCR, DFS, and OS in breast cancer patients who received NAC. In our opinion, the decision to apply NAC to the patient should still be made according to the molecular subtypes of the breast tumor. It should continue to be discussed in patient-based multidisciplinary sessions. In addition, although no correlation was found between the indices mentioned in our study and pCR, DFS, and OS, it would be helpful to continue studies on this subject considering the advantages of these indices, such as easy calculation and obtaining them from blood samples in routine practice.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of ıncidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
2. Derouane F, Van Marcke C, Berlière M, Gerday A, Fellah L, Leconte I, et al. Predictive biomarkers of response to neoadjuvant chemotherapy in breast cancer: current and future perspectives for precision medicine. Cancers (Basel). 2022;14:3876.
3. Kim HY, Kim TH, Yoon HK, Lee A. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in predicting neoadjuvant chemotherapy response in breast cancer. J Breast Cancer. 2019;22:425-38.
4. Corbeau I, Jacot W, Guiu S. Neutrophil to lymphocyte ratio as prognostic and predictive factor in breast cancer patients: a systematic review. Cancers (Basel). 2020;12:958.
5. Cullinane C, Creavin B, O'Leary DP, O'Sullivan MJ, Kelly L, Redmond HP, et al. Can the neutrophil to lymphocyte ratio predict complete pathologic response to neoadjuvant breast cancer treatment? A systematic review and meta-analysis. Clin Breast Cancer. 2020;20:e675-81.
6. Graziano V, Grassadonia A, Iezzi L, Vici P, Pizzuti L, Barba M, et al. Combination of peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. Breast. 2019;44:33-8.
7. Şahin AB, Cubukcu E, Ocak B, Deligonul A, Oyucu Orhan S, Tolunay S, et al. Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy. Sci Rep. 2021;11:14662.
8. Xu J, Ni C, Ma C, Zhang L, Jing X, Li C, et al. Association of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with ER and PR in breast cancer patients and their changes after neoadjuvant chemotherapy. Clin Transl Oncol. 2017;19:989-96.
9. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, et al. NCCN guidelines® insights: breast cancer, version 4.2023. J Natl Compr Canc Netw. 2023;21:594-608.

10. Residual Cancer Burden Calculator. MD Anderson Cancer Center; 2023 Available from: https://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3
11. Kaytaz Tekyol K, Gurleyik G, Aktaş A, Aker F, Tanrikulu E, et al. Pathological complete response to neoadjuvant chemotherapy in patients with breast cancer: the relationship between inflammatory biomarkers and molecular subtypes. Cureus. 2021;13:e14774.
12. Hiam-Galvez KJ, Allen BM, Spitzer MH. Systemic immunity in cancer. Nat Rev Cancer. 2021;21:345-59.
13. Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pretreatment systemic inflammation response index in patients with breast cancer treated with neoadjuvant chemotherapy as a useful prognostic indicator. Cancer Manag Res. 2020;12:1543-67.
14. Babbar P, Rudresha AH, Dasappa L, Abraham LJ, Babu MC, Lokesh KN, et al. Combined peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as a predictive biomarker for pathological complete response after neoadjuvant chemotherapy in triple-negative breast cancer patients. Oncol J India. 2022;6:8-13.
15. Dong J, Sun Q, Pan Y, Lu N, Han X, Zhou Q. Pretreatment systemic inflammation response index is predictive of pathological complete response in patients with breast cancer receiving neoadjuvant chemotherapy. BMC Cancer. 2021;21:700.
16. Yang G, Liu P, Zheng L, Zeng J. Novel peripheral blood parameters as predictors of neoadjuvant chemotherapy response in breast cancer. Front Surg. 2022;9:1004687.
17. Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pre-treatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. J Cell Mol Med. 2020;24:2993-3021.
18. Watanabe T, Hida AI, Inoue N, Imamura M, Fujimoto Y, Akazawa K, et al. Abundant tumor infiltrating lymphocytes after primary systemic chemotherapy predicts poor prognosis in estrogen receptor-positive/HER2-negative breast cancers. Breast Cancer Res Treat. 2018;168:135-45.
19. Araki K, Ito Y, Fukada I, Kobayashi K, Miyagawa Y, Imamura M, et al. Predictive impact of absolute lymphocyte counts for progression-free survival in human epidermal growth factor receptor 2-positive advanced breast cancer treated with pertuzumab and trastuzumab plus eribulin or nab-paclitaxel. BMC Cancer. 2018;18:982.
20. Suppan C, Bjelic-Radisic V, La Garde M, Groselj-Strele A, Eberhard K, Samonigg H, et al. Neutrophil/Lymphocyte ratio has no predictive or prognostic value in breast cancer patients undergoing preoperative systemic therapy. BMC Cancer. 2015;15:1027.
21. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164-72.
22. Yau C, Osdoit M, Van Der Noordaa M, Shad S, Wei J, De Croze D, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022;23:149-60.