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Research Article

Pan-immune-inflammation Value in Metastatic HER2-Positive Breast Cancer Patients

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Abstract

Objectives: The pan-immune-inflammation value (PIV) is an easily calculable immune marker based on blood laboratory tests to predict prognosis in cancer patients. The primary aim of this study is to evaluate the prognostic value of PIV in metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer (mBC) patients treated with dual block with pertuzumab.

Methods: This retrospective study evaluated the relationship between PIV and other prognostic markers, progression-free survival (PFS), and overall survival (OS) in HER2-positive metastatic BC patients treated with dual block with pertuzumab. PIV was calculated as follows: neutrophil count (10^9/L) × platelet count (10^9/L) × monocyte count (10^9/L)/ lymphocyte count (10^9/L).

Results: A total of 61 patients with mBC were included in this study. According to cutoff value for PIV, 31 (50.8%) and 30 (49.2%) patients fell into PIV-low <418,61 and PIV-high ≥418,61 groups, respectively. As a result of univariate analysis, high PIV was associated with worse outcome, which was statistically significant for both OS and PFS. Similarly, other IPMs were also statistically significantly associated with survival.

Conclusion: This study demonstrated that pre-treatment PIV may be a prognostic biomarker in metastatic HER2-positive BC patients treated with pertuzumab.

Keywords: Breast cancer, HER2-positive, PIV

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Breast cancer (BC) is the most common cancer in women worldwide. It is also the leading cause of cancer-related death. There were approximately 2,088,849 new cases of BC and 626,679 deaths worldwide in 2018.[1] Overexpression of human epidermal growth factor receptor 2 (HER2) is detected in approximately 15–20% of BCs. In addition, HER2-positive BC is typically associated with rapid clinical course and excessive disease aggression.[2] Trastuzumab is a humanized recombinant monoclonal antibody that targets HER2 to inhibit.[3] Pertuzumab is a new monoclonal antibody that came into use after trastuzumab. It is a recombinant humanized monoclonal IgG1 antibody that inhibits HER2 dimerization, resulting in more complete inactivation of HER2 signalling.[4] A more effective HER2 blockade was achieved as a result of using both monoclonal antibodies in combination with chemotherapy. The study that made this treatment a standard treatment for HER2-positive advanced BC patients is the Cleopatra study.[5] Inflammatory markers (IM) have been evaluated in most cancer types and have been found to be directly related to prognosis in dif-

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ferent tumor types.[6, 7] Similarly, these markers were evaluated in BC patients in different studies and found to be associated with prognosis. The most well-known of these IMs are the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and the monocyte-lymphocyte ratio (MLR). Another IM that has gained popularity especially recently is the pan-immune-inflammation-value (PIV).[8]

Here, hospital records of patients diagnosed with HER2+ advanced BC and treated with trastuzumab and pertuzumab were retrospectively reviewed. We investigated the potential role of PIV as a predictive and/or prognostic biomarker calculated by examining laboratory results.

Methods

Study Setting

This is a retrospective and single-center study conducted in HER2+ advanced BC patients who received chemotherapy-trastuzumab-pertuzumab therapy between April 2016 and December 2022. Eligibility criteria for the study were: (1) age ≥18; (2) pathologically confirmed diagnosis of unresectable, metastatic HER2+ advanced BC as defined as an immunohistochemistry (IHC) score for 3+ HER2 or a suspicious IHC score (2+) by in situ hybridization (ISH) HER2 gene amplification; (3) presence of peripheral blood counts including baseline (pre-treatment) absolute neutrophil, monocytes, lymphocyte, and platelet counts; (4) available information on prior treatments (especially prior HER2 treatments) in the presence of limited-stage disease; and (5) available information on the history of disease progression, newly developed sites of metastasis, and the patient's date of death. This study was approved by the Local Ethics Committee of Inonu University Medical Faculty Hospital (January 11, 2022; 2022/2880). Patient data were collected according to ethical principles for medical research involving human subjects accepted in the Declaration of Helsinki.

Objectives

The main aim of the study was to evaluate the relationship of PIV, NLR, and PLR obtained by basal peripheral blood parameters with progression-free survival (PFS)-the time between initiation of treatment and disease progression. The time between the patient's diagnosis and death due to any cause was defined as overall survival (OS). Tumor response to treatment was evaluated every 2 months (i.e., at approximately three treatment intervals). Positron emission tomography, computed tomography, and magnetic resonance imaging were used as imaging methods. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Evaluation of Biomarkers

In this study, the results of peripheral blood tests taken on the day of the start of treatment were examined. Absolute counts of neutrophils, lymphocytes, platelets and monocytes were recorded. PIV was calculated as follows: neutrophil count × platelet count × monocyte count/lymphocyte count. NLR was calculated as NLR=absolute neutrophil count/absolute lymphocyte count. PLR was calculated as PLR=absolute platelet count/absolute lymphocyte count. PNI was calculated using the formula (10 × albumin (g/L) + (0.005 × absolute lymphocyte count).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows Version 25.0 Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA. Descriptive statistics were presented as n and % for categorical variables, and Mean±SD, median (IQR) for continuous variables. ROC curve analysis was used to predict survival of various laboratory parameters. Kaplan–Meier method was used to compare survival times between various variables. Finally, multivariate Cox regression results are given on the risk of death from various clinical factors. $P<0.05$ was considered statistically significant.

Results

A total of 61 patients were evaluated in accordance with the inclusion and exclusion criteria. The median age of the patients was 60 (range 30–77). All patients in our study were female metastatic BC patients. While 31 (50.8%) of the patients included in our study were premenopausal, 30 (49.2%) patients were postmenopausal. The patients were also evaluated as the number of masses in the breast. While there were 30 (49.2%) patients with a single breast mass, there were 31 (50.8%) patients who were multicentric or multifocal. In terms of tumor location, while the mass was located in the right breast in 27 patients (44.3%), it was localized in the left breast in 33 patients (54.1%). One patient had bilateral BC. Pathological subtyping was interpreted as invasive ductal cancer in the vast majority of patients. Invasive ductal cancer was detected in 33 patients (54.1%), invasive lobular cancer in 4 (6.6%) patients, and mixed type BC in 2 (3.3%) patients. In the pathology results of 22 patients, BC subtyping was not performed. Pathology reports of the patients were examined in terms of hormone receptors. Estrogen receptor (ER) positivity was found in 40 (65.6%) patients, while ER was negative in 21 (34.3%) patients. Progesterone receptor (PR) positivity was found in 29 (47.5%) patients, while PR was negative in 32 (52.5%) patients. Patients were also evaluated for overexpression of HER2 from pathology

reports. As a result of the immunohistochemical examination, c-erb-B2 +2 positive was detected in 5 (8.2%) patients, and as a result of positive fluorescence ISH, they were treated with dual HER2 blockade. The remaining 56 patients (91.8%) were evaluated as +3 as a result of immunohistochemical examination and used systemic dual blockade therapy. The clinical and pathological data of these patients are shown in Table 1. In addition, information about tumor node metastasis (TNM) classification and metastasis sites of the patients included in our study are shown in Table 2. Inflammatory prognostic markers (IPM), NLR, PLR, and PIV, obtained from the laboratory parameters determined at the time of diagnosis of the patients in our study, were calculated separately. To evaluate the relationship between these values and survival, a cutoff value was calculated by ROC curve analysis. This analysis for obtaining the cutoff value is shown in Figure 1. As a result of this analysis, the cutoff value for NLR was 2.56; the cutoff value for PLR was 155.59, and the cutoff value for PIV was 418.61. Based on these cutoff values, the patients were divided into two groups and the survival results were evaluated separately. There are results that

Table 1. The Clinico-pathological features of the patients

	N (number of patients: 61)	%
Age		
Median	50	-
Range	30-77	-
Menopause Status		
Premenopausal	31	50,8
Postmenopausal	30	49,2
Tumor subtype		
Invasive Ductal Cancer	33	54
Invasive Lobular Cancer	4	6,6
Mixed Type Cancer	2	3,3
NOS	22	36,1
Number of Tumors		
Unifocal	30	49,2
Multifocal/Multicentric	31	50,8
Tumor Location		
Right	27	44,3
Left	33	54,1
Bilateral	1	1,6
Tumor Location		
Grade II	17	27,9
Grade III	15	24,6
Unspecified	29	47,5
E-cadherin		
Positive	21	34,4
Negative	2	3,3
Unspecified	38	62,3
Estrogen Receptor		
Positive	40	65,6
Negative	21	34,4
Progesterone Receptor		
Positive	29	47,5
Negative	32	52,5
Cerb-B2		
+2	5	8,2
+3	56	91,8
Ki-67 Index		
Median	30	-
Range	30-90	-

NOS: Not Otherwise Specified.

Table 2. TNM classification and Site of Metastasis

	N (number of patients: 61)	%
T Stage		
T1	5	8,2
T2	33	54,1
T3	19	31,1
T4	4	6,6
N Stage		
N1	22	36,1
N2	20	32,8
N3	19	31,1
Metastasis Site		
Lung	22	36,1
Liver	37	60,7
Bone	52	85,2
Skin	5	8,2
Brain	4	6,6
Adrenal Gland	13	21,3

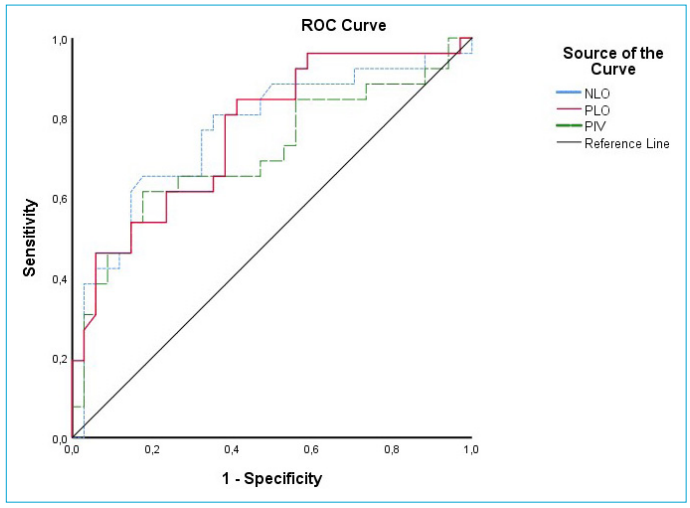

Figure 1. Roc Curve Analysis.

Table 3. Analysis of Predictive Values of PIV, NLR, and PLO on Mortality

Parameters	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	P
NLR	0.766	0,639-0,893	≥2,56	69,2	67,6	<0.001
PLR	0.766	0,645-0,888	≥155,59	65,4	64,7	<0.001
PIV	0.709	0,570-0,848	≥418,61	65,4	64,7	0.006

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; PIV: Pan-immune-inflammation-value.

include the analysis of the predictive values on mortality of all these IPMs and reach statistical significance. This information is shown in detail in Table 3. The relationship of IPMs with PFS and OS was investigated using cutoff values. There are differences in OS and PFS that reach statistical significance for both PIV and NLR. For PLR, there was statistical significance in terms of PFS, but no statistical significance was found for OS. The association of these IPMs with survival and statistical significance is shown in Table 4. Kaplan–Meier plots showing the relationship of PIV with both OS and PFS are shown in Figure 2. Another subject of our study was whether there were differences in survival between patients who had previously received trastuzumab in the adjuvant period and those who had never received trastuzumab before. Patients who previously received trastuzumab had a statistically significantly worse survival. As a result of univariate analyses, NLR, PIV, previous trastuzumab use, and patients with de novo metastases, which caused a statistically significant difference in survival, were re-evaluated in multivariate analysis. As a result of this multivariate analysis, statistical significance could not be reached for all these variables. Information including the results of the multivariate analysis is shown in Table 5.

Table 4. Association of NLR, PLR, ALP, and GGT with Survival (Month)

	Median	%95 CI		p
		Minimum	Maximum	
NLR (OS)				
<2,56	50	20,26	79,73	0.001
≥2,56	15	10,76	19,23	
NLR (PFS)				
<2,56	22	8,14	35,85	0.001
≥2,56	10	8,33	11,66	
PLR (OS)				
<156,56	NR	-	-	0.069
≥156,56	23	6,27	39,72	
PLR (PFS)				
<156,56	16	9,14	28,05	0.041
≥156,56	11	3,26	12,86	
PIV (OS)				
<418,61	NR	-	-	0.010
≥418,61	17	6,55	27,44	
PIV (PFS)			0.001	
<418,61	18	9,56	27,43	
≥418,61	11	5,28	11,71	

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; PIV: Pan-immune-inflammation-value.

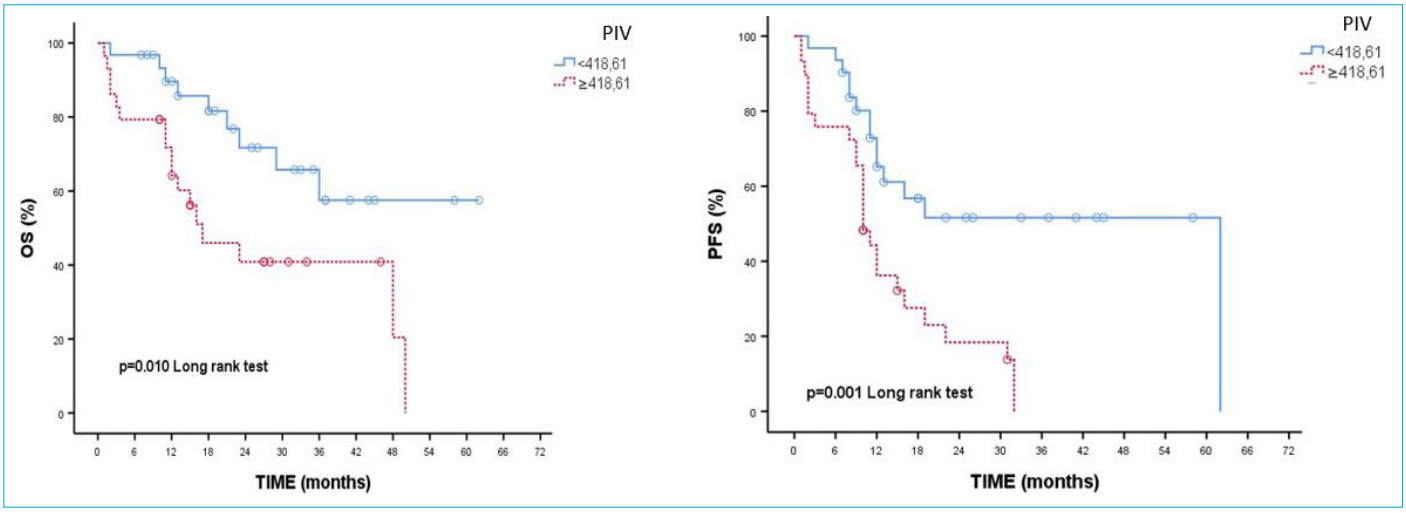

Figure 2. Relationship Between PIV and Overall Survival and Progression-Free Survival.

Table 5. Multivariate Cox Regression Results of OS

Parameters	Multivariate	
	HR (95%CI)	p
Previous trastuzumab treatment (No)	0.58 (0.24-1.38)	0.225
NLR (<2,56)	1.58 (0.59-4,24)	0.358
PIV (<418,61)	0.89 (0.34-2,29)	0.816
De novo metastases	1.34 (0.74-2.58)	0.921

NLR: Neutrophil-lymphocyte ratio; PIV: Pan-immune-inflammation-value.

Discussion

In general terms, the white blood cell count indicates the individual's systemic and/or local inflammation status.[9] Neutrophils are known to regulate the tumor microenvironment. It can also promote angiogenesis as well as tumor cell proliferation and migration by producing cytokines, chemokines, and growth factors.[10] M2 phenotype tumor-associated macrophages (TAMs) reside in the tumor microenvironment are derived from circulating monocytes. These TAMs promote metastasis and immunosuppression.[11, 12] This mechanism explains the association of increased peripheral monocytes with poor prognosis in cancer patients. Platelets, another peripheral blood element, also contribute to inflammation in favor of cancer through various mechanisms. For example, activated platelets form a protective layer around tumor cells. This layer protects the tumor cells from the cytolytic effect of immune cells. It also promotes tumor growth by secreting various growth factors such as TGF-β.[13, 14] In contrast to these blood cells, T lymphocytes are associated with the anti-tumor response.[15]

Numerous studies have previously been reported in the literature related to IPM. Similar to the patient population in our study, PLR was evaluated for patients treated with first-line trastuzumab in HER2-positive metastatic BC patients. As a result of this study, it was concluded that PLR is a predictive marker in HER2-positive metastatic BC patients treated with trastuzumab.[16] Another of the many studies in the literature has been evaluated for NLR. Patients treated with anti-HER2 in metastatic HER2-positive BC patients had a better anti-tumor response than those with lower NLR.[17] There are many studies on this IPM in the literature. The relationship of these markers with survival and treatment responses is now clearly known. Recently, PIV, an important marker, has also been associated with both treatment response and survival. PIV is a new biomarker obtained using different peripheral blood cells (neutrophils, platelets, monocytes, and lymphocytes). In fact, there are studies with the hypothesis that PIV, which can be evaluated as the synthesis of IPMs such as NLR, PLR, and MLR, can be a better marker candidate. In a recently published study completed by Ligorio et al., it was stated that PIV provides a better prediction of survival than other prognostic markers, NLR, PLR, and MLR.[8] There are retrospective studies in the literature with positive results for PIV not only in advanced stage BC patients but also in the early-stage BC patients. It was found to be more effective than other prognostic markers, especially in a study showing its relationship with pathological complete response after neoadjuvant therapy.[18] A recently published study analyzed post-operative survival for BC patients. In this study, PIV value and TNM staging system were compared in terms of OS. At the end of the study, it was concluded that PIV value was more effective than TNM in terms of determining OS.[19]

There are also different publications about PIV recently. In one of these articles, a negative correlation was found between PIV and treatment efficacy in first-line systemic treatment of metastatic malignant melanoma patients. In the related study, it was observed that patients with high PIV values had a worse response to both targeted therapies and immunotherapies compared to patients with low PIV values.[20]

We think that evaluation at the molecular and cellular level is as important as the TNM classification, both in making the treatment decision of cancer patients and in determining the criteria for following the patients for relapse. Molecular assessments are not widely used in most low-income countries due to their high cost. For this reason, IPM is particularly important for low-income countries where cost-effective use of available treatments is essential.

Conclusion

The present study has limitations such as including retrospective data, low number of patients, and inclusion of single center patients. Despite all these limitations, IPMs, especially PIV and NLR, are good prognostic markers in patients with advanced HER2-positive and BC treated with dual blockade.

Disclosures

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Inonu University Medical Faculty Hospital (January 11, 2022; 2022/2880).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.H., A.G.; Design – A.G.; Supervision – H.H.; Materials – A.G.; Data collection &/or processing – A.G.; Analysis and/or interpretation – A.G.; Literature search – A.G.; Writing – A.G.; Critical review – H.H.

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