A New Prognostic Index in Young Breast Cancer Patients

Hacer Demir[1], Ayse Demirci[2], Saliha Karagoz Eren[3], Ismail Beypinar[4], Sena Ece Davarcı[1] and Meltem Baykara[1]

[1]*Department of Medical Oncology, Afyon Health Sciences University School of Medicine, Afyonkarahisar, Turkey*
[2]*Department of Medical Oncology, Sakarya University Training and Research Hospital, Sakarya, Turkey*
[3]*Department of General Surgery, Kayseri City Hospital, Kayseri, Turkey*
[4]*Department of Medical Oncology, Eskişehir City Hospital, Eskişehir, Turkey*

ABSTRACT

Objective: To evaluate the prognostic role of pan immune-inflammation value (PIV) in young breast cancer patients.
Study Design: Descriptive study.
Place and Duration of Study: Department of Medical Oncology, Afyon University of Health Sciences, School of Medicine Hospital, Turkey, between January 2010 and December 2020.
Methodology: Patients who were under the age of 40 years at the time of diagnosis were included. Patients' characteristics and disease parameters were recorded. PIV was calculated according to (neutrophil x platelet x monocyte/lymphocyte, *i.e.* NxPxM/L) formula. Since a cut-off value with max sensitivity and specificity could not be obtained with ROC analysis, the median value of PIV was used as cut-off value. The relationship between PIV and pathological parameters was evaluated by ROC curves. The Kaplan-Meier method was used for OS and the log-rank test was used to evaluate the survival differences between the two groups, according to the optimal cut-off point.
Results: Based on the PIV cut-off value of 121 (49.8%) patients were in the low PIV and 122 (50.2%) patients were in the high PIV group. The patients in the high PIV group had a statistically significantly more advanced AJCC stage, and were younger patients. In the survival analysis, it was observed that the survival was worse in the high PIV group but this difference did not reach statistical significance (p=0.112).
Conclusion: Higher PIV levels at the time of diagnosis can be another prognostic marker. However, to clarify the PIV prognostic value, it needs to be validated in larger, multi-centre prospective clinical studies.

Key Words: *Breast cancer, Pan immune-inflammation value (PIV), Prognosis, Young women.*

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INTRODUCTION

Breast cancer is a global public health problem, and it is the most common cancer among women worldwide.[1] Although breast cancer is not common in young women, it accounts for approximately 40% of all cancers in women under 40 years.[2]

Mortality rates tend to decrease due to progress in diagnostic procedures that allow early diagnosis of breast cancer and the successes achieved in systemic treatment over the past years. The risk of developing breast cancer increases with age; however, breast cancer can also develop in young women, *i.e.* under 40 years. Young women with breast cancer diagnosed before the age of 40 years are 6.6% of all cases; while those under 35 years, constitute 2.4%.[3,4]

Correspondence to: Dr. Hacer Demir, Department of Medical Oncology, Afyon Health Sciences University School of Medicine, Afyonkarahisar, Turkey
E-mail: drhacerdemir@gmail.com
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Breast cancer has a more aggressive course in cases under the age of 40, and they have a higher death rate compared to the older counterpart; and the tumour generally tends to be larger, higher histologic grade, more hormone receptor (HR) negative, and epidermal growth factor 2 (HER-2) being positive. In younger patients, the frequency of triple-negative (ER (-) PR (-) HER2 (-)) tumours also high.[5,6]

Since breast cancer is a heterogeneous tumour with different genomic subtypes, it differs in prognosis. Tumour size, stage, histological subtype, lymph node involvement, hormone receptor (HR) status, epidermal growth factor 2 (HER2) status, grade are histopathological factors used to determine survival and prognosis. Also, age is accepted as an independent prognostic factor in breast cancer patients.[7] However, up-to-date and reliable prognostic parameters are still needed to personalise the treatment of breast cancer patients and improve survival.

Tumour microenvironment consists of neutrophils, monocytes, lymphocytes, platelets and plays an important role in tumor development and progression along with cancer-associated inflammation.[8,9] It was shown that systemic inflammatory responses include DNA damage, angiogenesis and, tumor inva-

sion and migration. Inflammatory cells such as neutrophils, lymphocytes, monocytes, platelets and parameters such as neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MRL), platelet/lymphocyte ratio (PRL), which are used routinely, are thought to be indicators of systemic inflammatory and recommended as a prognostic factor in many cancers.[9,10]

The pan-immune-inflammation value (PIV) is a parameter calculated using platelet, neutrophil, monocyte, and lymphocyte counts, reflecting the balance between host immune and inflammation status. PIV has previously only been studied in metastatic colorectal cancer patients and included in Valentino and TRİBE studies, and has been shown to be prognostic. As a result, the authors concluded in the study that PIV predicted survival better than other well-known immune indices.[11]

In recent years, studies that are evaluating the prognostic effect of inflammatory biomarkers in breast cancer patients, have shown that indices such as (NLR), (LMR), (PLR) are prognostic factors.[12,13] However, there are no studies on PIV in breast cancer yet. It was thought that PIV could predict a better prognosis than other inflammatory indices.

The aim of this study was to evaluate the prognostic capacity of this new biomarker, The PIV, its relationship with other prognostic parameters, and the effect on survival in patients diagnosed with breast cancer before the age of 40 years.

METHODOLOGY

This descriptive study, which was conducted retrospectively, included patients who were diagnosed with breast cancer between 2006 and 2020, aged 40 years and younger, and admitted to the Medical Oncology Outpatient Clinic. The study was initiated after obtaining approval from the Ethics Committee of the University. After obtaining written consents from the patients, histopathological, clinical, and file data were recorded retrospectively.

The patients included in the study consisted of patients histopathologically diagnosed with breast cancer, between the age of 18 and 40 years, with complete file information and regular follow-ups. Exclusion criteria were patients with active infection or using steroids during hemogram, ductal or lobular carcinoma *in-situ*, patients with insufficient follow-up and file data, patients with acute or chronic inflammatory disease, patients with the haematological disease, patients without hemogram data at diagnosis, and male patients with breast cancer.

Patients' age, histology, tumour size, lymph node metastasis status, histological grade, ER, PR, HER-2 status, Ki-67 index, operation type, and treatment characteristics were obtained from the files and by reviewing the hospital information system. PIV was calculated with the formula (neutrophil x platelet x monocyte / lymphocyte) using the platelet (10^3/μL), neutrophil (10^3/μL), monocyte (10^3/μL) and lymphocyte (10^3/μL) counts obtained from the preoperative hemogram examinations. The PIV cut-off value was calculated by performing ROC analysis. Since a cut-off value with maximum sensitivity and specificity could not be obtained, the median value of PIV was used. Disease-free survival (DFS) was calculated as the time from diagnosis to the first disease recurrence. Overall survival (OS) was calculated as the time from the date of diagnosis to death from any cause or the last control date.

The SPSS version 26.0 software (SPSS; Chicago, IL, USA) programme was used in all analyses, and a p-value of <0.05 was considered statistically significant. Descriptive statistics including patient age, tumour stage, clinical presentation, histopathological type, grade, immune histochemical findings, Ki 67 status were presented as frequencies and percentages of categorical variables and median (minimum-maximum) of quantitative variables. A Chi-square test was employed for categorical variables. The relationship between PIV and pathological parameters was evaluated by ROC curves. The Kaplan-Meier method was used for OS and the log-rank test to evaluate the survival differences between patients divided into two groups, according to the optimal cut-off point.

RESULTS

Approximately 4000 patients diagnosed with breast cancer in three medical oncology centres (clinic) were reviewed at first. Files of 253 patients under the age of 40 years at the time of diagnosis were accessed; 243 patients, whose preoperative hemogram values could be reached, were included in the study. The clinicopathological characteristics of the patients are shown in Table I.

The median age in the study was 36 years, and the youngest patient was 21 years of age. At the time of diagnosis, 131 patients were under the age of 35 years.

Median body mass index (BMI) was 26.35 (19-43.56) Kg/m^2. Smoking history was present in 9.5% (n = 23). Forty-six patients (18.9%) had a family history of breast cancer, and only two patients were postmenopausal period. In 210 patients (86.4%), the first presentation symptom was a palpable mass, and it was the most frequent mode of presentation. Only 6 (2.5%) were diagnosed with routine screening, and in 15 (6.2%) patients, breast cancer was diagnosed during the controls performed for any reason. Considering histological subtypes, most of the patients had invasive ductal carcinoma 218 (89.7%), five patients (2.1%) had medullary carcinoma, five (2.1%) patients had invasive lobular carcinoma, and 15 patients had other histological subtypes.

The frequency of mass localised in the left breast was higher (137 patients 53.3%). Pathologically, in immunohistochemical evaluation, 197 (81.1%) of the patients were ER (+), 177 (72.8 %) were PR (+) and 71 (29.2%) were HER-2 (+). The number of triple-negative patients was 29 (11.9%). When the histological grades were examined, Grade 2 (41.2%) disease was the most common. Lymphovascular invasion was present in 82 (33.7%) of the patients; the perineural invasion was detected in 38 (15.6%) patients. When evaluated according to the stages of T and N, the most common T stage was T2 (116 patients % 47.7), while the most common N stages were N1 (80 patients, 32.9%). According to the AJCC 7th staging system, the number of stage 1/2/3 patients were 40 (16.5%) / 121 (49.8%) / 57 (23.5%), respectively; and 9.1% of the patients were at the metastatic stage at the time of

diagnosis. The number of breast-conserving surgery and modified radical mastectomies were similar in patients who underwent surgery (48.6% *vs.* 44.4%). Adjuvant radiotherapy (RT) and chemotherapy (CT) were used in 76.5% and 70% of patients, respectively; and 189 patients (77.8%) were given adjuvant hormone therapy.

Table I: General characteristics of the study group.

	Number	%
Age		
≤35	131	53.9%
>35	112	46.1%
Family history		
Present	46	18.9%
Absent	158	65%
Histological type		
Invasive ductal	218	89.7%
Invasive lobular	5	2.1%
Medullary	5	2.1%
Other	15	6.2%
Breast side		
Right	111	45.7%
Left	129	53.1%
Hormone receptor status (HR)		
HR +	197	81.1%
HR -	44	18.1%
HER-2 status		
Her-2 +	71	29.2%
Her-2 -	170	70.0%
AJCC stage at diagnosis		
I	40	16.5%
II	121	49.8%
III	57	23.5%
IV	22	9.1%
Lymph Node status		
N0	85	43.3%
N1	75	38.2%
N2	21	10.7%
N3	15	7.6%
T stage		
T1	53	21.8%
T2	116	47.7%
T3	27	11.1%
T4	4	1.6%
Type of surgery		
BCS (breast conservative surgery)	118	48.6%
MRM (modified radical mastectomy)	108	44.4%
Adjuvant Radiotherapy		
Given	186	76.5%
Not Given	46	18.9%
Adjuvant chemotherapy		
Given	170	70.0%
Not given	61	25.1%
Recurrence		
Present	34	14.0%
Absent	194	79.8%
Grade		
I	38	15.6%
II	100	41.2%
III	67	27.6%
PIV		
≤301	121	49.8%
>301	122	50.2%
Ki67		
≤30	114	59.1 %
>30	79	40.9 %

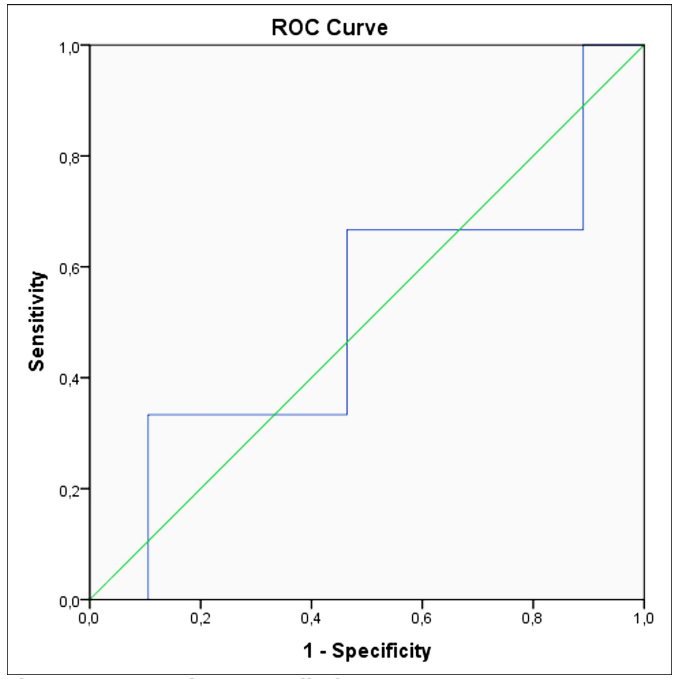

Figure 1: ROC curve for PIV cut-off value.

The most commonly used hormone therapy was tamoxifen and LHRH (136 patients, 56%). Neoadjuvant therapy was given to 75 (30.9%) patients. The median Ki 67 level was 25 (1-90) in 193 patients with Ki67 data available, while there were 114 (59.1%) patients with Ki 67 levels below 30, and 79 (40.9%) patients with Ki 67 levels above 30. Recurrence was observed in 34 patients during follow-up, and recurrence/metastasis development was detected in 22 (9.1%) patients after adjuvant therapy. Three patients had second primary breast cancer, only 13 (5.3%) patients died in the study group. The stages of the deceased patients at the time of diagnosis consisted of stage 3 and stage 4 patients (69.2%).

In the study group, since a significant value with maximum sensitivity and specificity could not be obtained with ROC analysis (Figure 1), the median value was taken as the optimum cut-off. Based on the PIV cut-off value of 301, 121 (49.8%) patients were in the low PIV group, and 122 (50.2%) patients were in the high PIV group.

When the relationship between prognostic factors of the patients and PIV was examined, no statistically significant relationship was observed between age, hormone receptor status, Her-2 status, histological subtype, ER, PR, HER-2 status, grade, Ki 67 status, lymph node involvement, and PIV. Although it did not reach statistical significance according to PIV levels, it was observed that patients with high PIV values had more advanced lymph node stage and T stage, were diagnosed at the more metastatic stage and were younger (Table II).

However, in the survival analysis, there was a difference in overall survival between the low and high PIV groups, but this difference did not reach statistical significance (p=0.112). Survival was worse in the high PIV group (Figure 2, Kaplan-Meier analysis). The 3-year and 5-year survival rates were 93% and 93% in the low PIV group and 89% and 71% in the high PIV group (Figure 3).

Table II: Clinicopathologic characteristics of the patients, according to PIV groups.

Category	PIV ≤301 (121)	PIV >301 (122)	p-value
Age (n/%) ≤35 >35	 65 (49.6) 56 (50.0)	 66 (50.4) 56 (50.0)	P=0.953
ER Status (n/%) Positive Negative	 96 (48.7) 24 (54.5)	 101 (51.3) 20 (45.5)	P=0.486
PR status (n/%) Negative Positive	 34 (53.1) 86 (48.6)	 30 (46.9) 91 (51.4)	P=0.534
HER-2 status (n/%) Negative Positive	 81 (47.6) 39 (54.9)	 89 (52.4) 32 (45.1)	P=0.303
AJCC stage (n/%) Stage I Stage II Stage III Stage IV	 17 (42.5) 74 (61.2) 23 (40.4) 6 (27.3)	 23 (57.5) 47 (38.8) 34 (59.6) 16 (72.7)	**P=0.004**
Grade (n/%) Well-differentiated Moderately differentiated Poorly differentiated	 23 (60.5) 45 (45.0) 36 (53.7)	 15 (39.5) 55 (55.0) 31 (46.3)	P=0.222
Lymph Node Status (n/%) N0 N1 N2 N3	 42 (49.4) 43 (57.3) 10 (47.6) 3 (20.0)	 43 (50.6) 32 (42.7) 11 (52.4) 12 (80.0)	P=0.070
Breast side (n/%) Right Left	 52 (46.8) 66 (51.2)	 59 (53.2) 63 (48.8)	P=0.505
Surgery Type (n/%) BCS MRM	 61(51.7) 57 (52.8)	 57 (48.3) 51 (47.2)	P=0.871
Ki 67 Status (n/%) ≤30 >30	 54 (47.4) 43 (54.4)	 60 (52.6) 36(45.6)	P=0.335
Histological Type (n/%) Invasive ductal carcinoma Invasive lobular carcinoma Medullary carcinoma Other	 112 (51.4) 1 (20.0) 4 (80.0) 4 (26.7)	 106 (48.6) 4 (80.0) 1 (20.0) 11 (73.3)	P=0.071

PIV: Pan-immune- inflammationindex, ER: Estrogenreceptor, PR: Progesteronereceptor, BCS: Breast conservativesurgery, MRM: Modifiedradicalmastectomy.

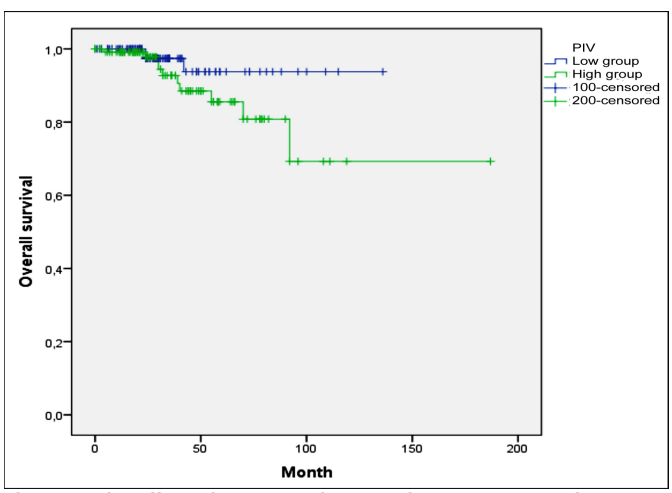

Figure 2: The effect of PIV on OS in young breast cancer patients.

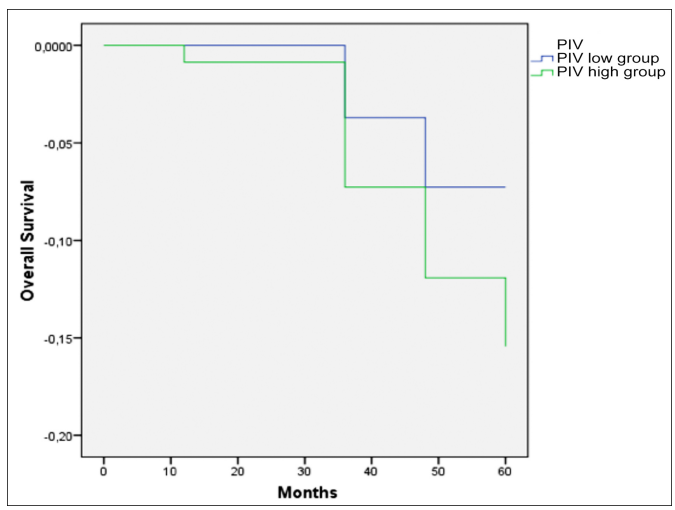

Figure 3: 3 years and 5 years survival, according to the PIV groups.

DISCUSSION

In the present study, the aim was to investigate the prog-

nostic significance of PIV in young breast cancer patients. There was a statistically significant association between high PIV and AJCC stage, and a shorter overall survival with the high-value group, which did not reach statistical signifiance. When disease-free survival rates of 3 and 5 years were evaluated, they were also shorter in the high PIV group.

Solid tumours consist of neoplastic cells, non-malignant stromal cells, and hematopoietic cells. Inflammatory cells and mediators, such as cytokines released from them, are also part of the tumour microenvironment. The role of cancer-associated inflammation in cancer development and progression has been demonstrated in various studies.[14,15]

The connection between inflammation and cancer can be in two ways. In some cancers, inflammation development precedes the development of malignancy, while in others, various genetic and oncogenic changes create an inflammation environment that triggers cancer development. Inflammation by any means contributes to the prolongation of the life span of malignant cells, development of angiogenesis and metastasis, impairs adaptive immunity, changes the response to treatment. Consequently, inflammation causes shorter survival and poor prognosis.[16,17]

Recently, the relationship between various inflammatory indices such as neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII) calculated by inflammatory cells in peripheral blood and prognosis has been shown in many cancers.[18-21] In studies conducted by different investigators, various systemic inflammatory markers are prognostic in patients with breast cancer.[13,22,23]

PIV is a new inflammation-based marker, whose prognostic impact has been investigated in patients with metastatic colorectal cancer receiving first-line chemotherapy and biologic agent for the first time. Fuca *et al*. reported that patients who have high PIV experienced worse PFS and OS compared to the low group.[11]

According to the current knowledge, this study is the first one to comprehensively evaluate the prognostic value of PIV in breast cancer patients. These findings show that the preoperative high PIV is associated with shorter DFS and OS in young breast cancer patients, although it does not reach statistical significance.

This study has limitations in some aspects. The first is that it has a retrospective design; secondly, it has a short follow-up period; and the third is that all the patients were under the age of 40 years. At the time of diagnosis, more intensive treatments can be planned by considering the PIV status and classical prognostic indicators in young breast cancer patients.

More significant results can be obtained in studies when more homogeneous, and more specific subgroups are included. While PIV is a candidate to be an independent predictor in young breast cancer patients, its sensitivity and specificity are not high. Prospective randomised and well-designed studies are needed for the optimisation of the appropriate cut-off value.

CONCLUSION

PIV an index, based on peripheral inflammation can be used as an easy-to-apply and easily repeatable, inexpensive, non-invasive, and effective marker to show the prognosis in, young breast cancer patients. The present findings suggest that patients with higher PIV levels may have a worse prognosis at the time of diagnosis. However, to clarify the PIV prognostic value, it needs to be validated in larger, multi--centre clinical studies.

ETHICAL APPROVAL:

The study was approved by local Ethics Committee of Afyonkarahisar Health and Science University (Approval No: 2021/3 2011-KAEK-2).

PATIENTS' CONSENT:

Informed consents were obtained from the patients to anonymise and publish the data on this case.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SD: Study concept, study design.
HD, AD, SKE: Data collection.
IB, MB, SED, SKE: Quality control of data and algorithms.
IB, AD: Statistical analysis.
HD, SKE: Manuscript preparation.
All authors were involved in the critical review, and revised the manuscript for important intellectual content.

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