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ORIGINAL RESEARCH

High Levels of SII and PIV are the Risk Factors of Axillary Lymph Node Metastases in Breast Cancer: A Retrospective Study

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Purpose: To investigate the predictive value of systemic immune-inflammation-index (SII) and Pan-Immune-Inflammation-value (PIV) for axillary lymph node (ALN) metastasis in patients with breast cancer.

Patients and Methods: We retrospectively collected data of 247 patients with invasive breast from the Affiliated Hospital of Jiangnan University. The state of axillary lymph node (ALN) metastasis was confirmed by pathological diagnosis. Clinicopathological data (age, ER, PR, HER2, Ki67 expression levels, diapause status, weight, histological grade, vascular invasion, and state of axillary lymph node) were compared between differences of SII and PIV groups and an association between clinical indexes and ALN metastasis was evaluated.

Results: The cut-off values of SII and PIV were 320.04 and 92.01, respectively. The significant difference between vascular invasion (P=0.023) and axillary lymph node metastases (P<0.001) in the high and low SII levels. Significant differences were observed in tumor size (p=0.024), PR expression level (P=0.033) and the status of axillary lymph node metastases (p<0.001) between the high PIV group and the low PIV group. Univariate analysis showed that vascular invasion, tumor size, Ki67 expression level, SII, and PIV were significantly correlated with axillary lymph node metastases (p<0.05). Then, multivariate analysis revealed that the vascular invasion (p<0.001), HER2 expression levels (p<0.047), SII (p<0.001) and PIV (p<0.030) were risk factors for axillary lymph node metastases.

Conclusion: High levels of SII, PIV, LVI, and HER2 are the risk factors for axillary lymph node metastases in breast cancer patients.

Keywords: breast cancer, systemic immune-inflammation-index, axillary lymph node metastases, pan-immune-inflammation-value

Introduction

Breast cancer is the most common cancer, with an incidence of about 24.5% of malignant tumors and a mortality rate of 15.5%, which is one of the leading causes of cancer death in women worldwide.[1] Axillary lymph node (ALN) metastasis is a key factor for treatment and prognosis in breast cancer patients. At present, sentinel lymph node biopsy (SLNB) is a standard surgical procedure that can be used to diagnose axillary lymph node status in breast cancer patients. However, some studies believe that the false-negative rate of SLNB is still a problem, affecting the selection of surgical modality and comprehensive treatment regimens at a later stage.[2] Meanwhile, when ALN is located around blood vessels and located deeply, patients may experience postoperative complications after the SLNB, such as hematoma, upper limb numbness and lymphedema, which seriously affects the quality of life in breast cancer patients. Consequently, some disadvantages of SLNB cannot be ignored.[3,4] In addition, studies have found that fluorodeoxyglucose PET/CT (FDG-PET/CT) predicts the status of ALN of breast cancer, however, has serious side effects of radiation.[5,6] Precise axillary lymph node evaluation before surgery is important to choose a proper therapeutic regimen and estimate the prognosis of

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breast cancer. Therefore, finding no trauma and convenient methods to accurately assess ALN status before surgery is greatly significant for the treatment of breast cancer patients.

The tumor immune microenvironment has become increasingly prominent in recent years. Inflammatory mediators and inflammatory cells are crucial elements of the neoplastic microenvironment. Chronic systemic inflammation is related to the occurrence, development and metastasis of tumors.[7] Recently, studies have found that systemic immune-inflammation-index (SII) and Pan-Immune-Inflammation-value (PIV) can reflect immune and systemic inflammatory responses, and be associated with the prognosis of different types of cancer, such as cervical cancer,[8] endometrial cancer[9] and colorectal cancer.[10,11] In addition, studies have revealed that SII and PIV are also closely associated with poor prognosis in breast cancer patients.[12,13] However, the relationship between SII, PIV and ALN status is unclear. So, the study is aimed to investigate the predictive value of SII and PIV for ALN metastasis in patients with breast cancer.

Materials and Methods

Study Design

The current study retrospectively analyzed patients with invasive breast cancer who underwent primary at the Affiliated Hospital of Jiangnan University from January 2021 to 2021 December. Inclusion criteria: (1) All of those patients with invasive breast cancer had been confirmed by pathological evaluations. (2) The presence or absence of axillary lymph node metastasis was confirmed by pathological diagnosis. (3) All participants are females in our study. Exclusion criteria: (1) Patients with incomplete clinical information were excluded. (2) Patients who had undergone neoadjuvant therapy before surgery were excluded. (3) Following diagnosis, patients with other types of malignancies or severe diseases were not included. The research complies with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Affiliated Hospital of Jiangnan University (JNMS01201800139). All data are anonymous and aggregated, so the requirements for informed consent are waived.

Data Collection and Definitions

Demographic, clinical as well as pathological characteristics data of 247 patients were retrieved from Affiliated Hospital of Jiangnan University databases. The information included age, gender, diapause status, weight, histological grade, vascular invasion (VI), estrogen receptor (ER), estrogen receptor (PR), human epidermal growth factor receptor2 (HER2), Ki67, white blood cell counts (WBC), neutrophil (NEs), monocytes (MO), platelet (PLT), lymphocytes (Lyms), serum tumor marker tests (CA125, CA153, CA199) and state of an axillary lymph node. SII was calculated based on the following formula: platelet count × neutrophil count/lymphocyte count. PIV = platelet count × neutrophil count × monocytes count/lymphocyte count. All patient's blood samples were collected in the week before surgery.

Immunohistochemical Assessment

Estrogen and progesterone receptors were detected by IHC, staining of ≥1% was determined as positive, and <1% was negative.[14] According to the HER2 expression status, 0~+ was defined as negative; otherwise, they were defined as positive; If the result was ++, then further FISH test should be performed, and amplified type means the positive result, unamplified type means negative result.[15] The cutoff of ki67 expression level was established at 20%, if immunostaining occurred in <20% and ≥20% of epithelial tumor cells, Ki67 expression was classified as low and high proliferative activity, respectively.[16]

Statistical Analysis

SPSS26.0 was used to perform all statistical analyses. Continuous variables were analyzed by Student's *t*-tests or Mann–Whitney *U*-tests. Categorical data were analyzed using the chi-squared tests or Fisher's exact tests. The data was divided into metastatic and non-metastatic groups by the clinical traits of axillary lymph nodes. Receiver operating characteristic (ROC) curve analysis was performed. The area under the curve (AUC) and specificity with 95% confidence intervals were calculated. SII and PIV cutoff values were calculated based on the maximum Youden index, and patients were divided into high-level and low-level groups based on the cutoff values. The relationship between SII and PIV and

clinicopathological factors were analyzed using the chi-square tests. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for axillary lymph node metastasis. $P<0.05$ indicated the difference had statistical significance.

Result

Baseline Characteristics

A total of 247 study subjects were enrolled in the study. Essential characteristics of breast cancer patients are displayed in Table 1. The age range of participants was from 29 to 92 with a median of 56 years. Among all patients, 67 (27.1%) patients were pathologically diagnosed with axillary lymph node metastasis.

SII and PIV cut-off value. In the present study, Mean SII and PIV were 405.61±15.48 and 115.92±8.11 in patients with breast cancer, respectively. ROC curves were plotted based on the relationship between SII, PIV and axillary lymph node metastasis. The results revealed that the area under the curves for SII and PIV were 0.769 and 0.651, respectively. The SII and PIV values corresponding to the maximum of the Youden index were taken as the optimum cut-off point, and the cut-off values of SII and PIV were 320.04 and 92.01, respectively, with a sensitivity of 95.5% and 76.1%, respectively (Figure 1).

Based on the cut-off value of SII and PIV, patients were divided into a high-SII group (SII≥320.04), a low-SII group (SII<320.04), a high-PIV group (PIV≥93.01) and a low-PIV group (PIV<93.01). The significant difference between vascular invasion ($P=0.023$) and axillary lymph node metastases ($P<0.001$) in the high and low SII levels. But no significant differences were observed in age, tumor size, histological grading, and ER, PR, Ki67 and HER2 expression ($P>0.05$) (Table 2). Significant differences were observed in tumor size ($p=0.024$), PR expression level ($P=0.033$) and the status of axillary lymph node metastases ($p<0.001$) between the high PIV group and the low PIV group. However, no significant association with age, vascular invasion, histological grading, ER, Ki67 index, and HER2 expression between the two PIV groups ($P>0.05$) (Table 3).

In the present study, Univariate analysis showed that vascular invasion, tumor size, Ki67 expression level, SII, and PIV were significantly correlated with axillary lymph node metastases ($p<0.05$), but age, weight, histological grading, diapause status, CA125, CA153, CA199, ER, PR, HER2 expression level was not relevance to axillary lymph node metastases ($p>0.05$) (Table 4). Significant factors from the univariate analysis were included in the multivariate analysis revealing that the vascular

Table 1 Baseline Characteristics of Breast Cancer Patients

Parameter	Case	Constituent Ratio (%)
Age	≤55.121	49
	>55.126	51
Tumor size(cm)	≤2.131	53
	>2.116	47
ALN status	Negative 180	72.9
	Positive 67	27.1
ER	Negative 57	23.1
	Positive 190	76.9
PR	Negative 89	36
	Positive 158	64
HER-2	Negative 184	74.5
	Positive 63	25.5
Ki67	Low 64	25.9
	High 183	74.1
VI	No 175	70.9
	Yes 72	29.1

Abbreviations: ALN, axillary lymph node; ER, estrogen receptor; PR, estrogen receptor; HER2, human epidermal growth factor receptor2; VI, vascular invasion.

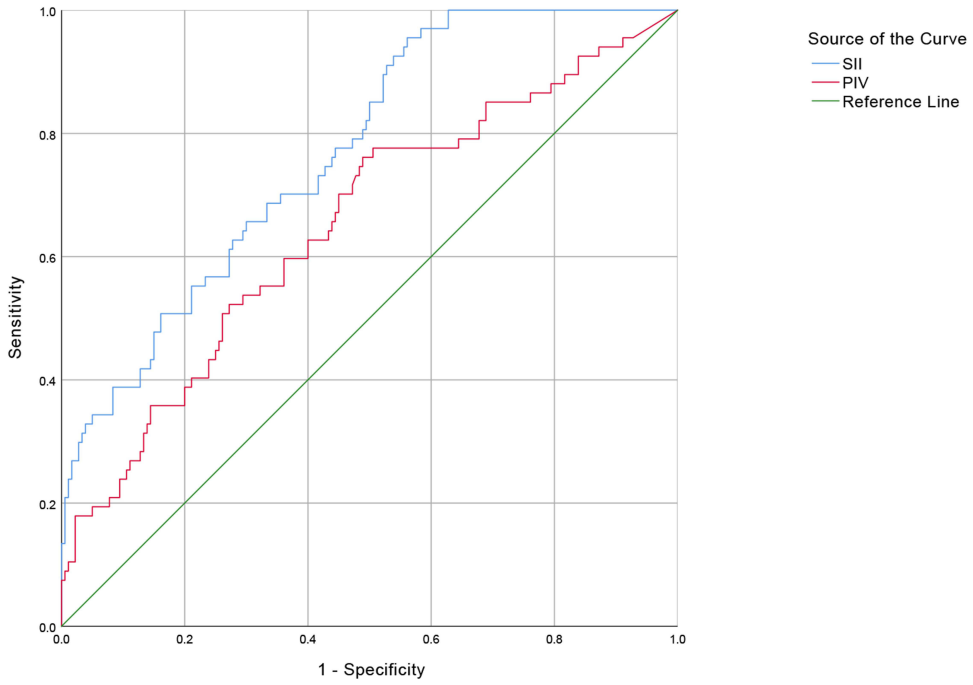

Figure 1 Relationship between the levels of SII, PIV and axillary lymph node metastasis before preoperative.

invasion (p<0.001), HER2 expression levels (p<0.047), SII (p<0.001), and PIV (p<0.030) were independent risk factors for axillary lymph node metastases (Table 5), however, but there was no significant difference in age, Ki67, ER and PR expression levels (p>0.05).

Table 2 The Associations of the Level of SII with Clinicopathological Characteristics

Parameter	SII<320.04	SII≥320.04	P
Age	≤55.38	83	0.649
	>55.43	83	
ER	Negative 17	39	0.331
	Positive 63	127	
PR	Negative 32	56	0.207
	Positive 48	110	
HER-2	Negative 60	124	0.916
	Positive 21	42	
Ki67	Low 24	40	0.351
	High 57	126	
VI	No 65	110	0.023
	Yes 16	56	
Tumor size(cm)	≤2.49	82	0.101
	>2.32	84	
ALN status	Negative 79	101	<0.001
	Positive 2	64	
Histologic stage	I 2	7	0.419
	II 48	85	
	III 28	71	

Abbreviations: ALN, axillary lymph node; ER, estrogen receptor; PR, estrogen receptor; HER2, human epidermal growth factor receptor2; VI, vascular invasion.

Table 3 The Associations of the Level of PIV with Clinicopathological Characteristics

Parameter	PIV<93.01	PIV≥93.01	P
Age	≤55.56	65	0.295
	>55.50	76	
ER	Negative 26	30	0.348
	Positive 79	111	
PR	Negative 46	42	0.033
	Positive 59	99	
HER-2	Negative 79	105	0.991
	Positive 27	36	
KI67	Low 28	36	0.875
	High 78	105	
VI	No 81	94	0.095
	Yes 25	47	
Tumor size(cm)	≤2.65	66	0.024
	>2.41	75	
ALN status	Negative 90	90	<0.001
	Positive 16	51	
Histologic stage	I 3	6	0.918
	II 58	75	
	III 42	57	

Abbreviations: ALN, axillary lymph node; ER, estrogen receptor; PR, estrogen receptor; HER2, human epidermal growth factor receptor2; VI, vascular invasion.

Discussion

Axillary lymph node metastases are the most important factor for breast cancer diagnosis and prognosis and have significant implications in the utility of protocol for clinical application. Currently, few studies have explored associations between blood indicators and axillary lymph node metastases in breast cancer. In this study, we sought to decipher the connection between preoperative inflammatory indicators and axillary lymph node metastases. Our study is the first found that elevated SII and PIV were independent risk factors for axillary lymph node metastases in patients with breast cancer.

In recent years, the association between inflammation and tumors has become a research hotpot, and studies have found that the inflammatory immune microenvironment plays a major role in tumor growth and metastasis.[17,18] NEs, PLT, MO and Lyms are the main hematological indicators reflecting systematic inflammation. NEs promote tumor invasion by secreting matrix metalloproteinase, vascular endothelial growth factor, IL-6 and IL-8;[19] MO can be further polarized into tumor-associated macrophages (TAMs), which plays an important part in the tumor microenvironment by promoting tumor progression, metastasis, and immune escape;[20] besides, the PLT by secreting tumor growth factors and angiogenic factors, thus facilitating the infiltration and metastasis of tumor cells.[21] Conversely, lymphocytes play an important role in anti-tumor immune responses by secreting IL-17 and initiating the cytotoxic immune response.[22]

Several studies have reported that SII was a comparatively novel indicator based on the account of NEs, Lyms and PLT, and potential prognostic markers for various tumors. Xin Hua showed that preoperative SII score can independently predict postoperative OS and DMFS in breast cancer.[23] Cong Jiang suggested that pretreatment SII is significantly associated with OS, and SII is superior to NLR and PLR in breast cancer patients receiving neoadjuvant chemotherapy.[24] Further, the preoperative PIV, a new blood-based biomarker that involves diverse peripheral blood immune cell subsets: neutrophil, platelet, monocyte, and lymphocyte, is the potential to represent comprehensively a patient's immunity and systemic inflammation. Birol Ocak found that PIV appears to be a very strong predictor of pathologic complete response (PCR) and survival in breast cancer patients, and the low PIV group patients have significantly longer DFS and OS than the high PIV group.[13] However, the association between SII and PIV with axillary lymph node metastases is unclear. We found that high SII and PIV values

Table 4 Relationship Between ALN and Clinicopathological Factors

Parameter	No-LNM	LNM	P
Age	56.08 (54–57)	56.07 (53–59)	0.708
Weight	63.0 (57.43–68.61)	59.8 (57.94–61.75)	0.994
Menopause status	Premenopausal 112	37	0.318
	Postmenopausal 68	30	
ER	Negative 44	12	0.384
	Positive 135	55	
PR	Negative 65	23	0.698
	Positive 114	44	
HER-2	Negative 138	42	0.199
	Positive 72	21	
Ki67	≤20Lowexpression 55	9	0.006
	>20Higerxpression125	58	
VI	No 149	26	<0.001
	Yes 31	41	
Tumor size(cm)	≤2.107	24	<0.001
	>2.73	43	
Histologic stage	I7	2	0.128
	II104	29	
	III64	35	
SII	≤320.04 (79)	2	<0.001
	>320.04 (101)	65	
PIV	≤93.01 (90)	16	<0.001
	>93.01 (90)	51	
CA125U/L	10.54 (8.29–12.80)	13.49 (6.00–20.98)	0.658
CA153 U/L	8.22 (7.70–8.73)	11.91 (7.76–16.06)	0.058
CA199 U/L	10.91 (9.80–12.02)	11.93 (10.00–13.86)	0.416
	56.08 (54–57)	56.07 (53–59)	0.708

Abbreviations: ALN, axillary lymph node; ER, estrogen receptor; PR, estrogen receptor; HER2, human epidermal growth factor receptor2; VI, vascular invasion; SII, platelet × count × neutrophil count/lymphocyte count; PIV, platelet count × neutrophil count × monocytes count/lymphocyte count.

Table 5 Multivariate Analysis of ALN and Clinical Pathological Factors

	B	SE	wals	sig	Exp(B)
Age	0.013	0.015	0.745	0.388	1.013(0.983–1.004)
ER	−0.777	0.63	1.520	0.218	0.460(0.134–1.582)
PR	−0.125	0.574	0.048	0.827	0.882(0.287–2.716)
Her-2	−0.882	0.443	3.955	0.047	0.414(0.174–0.987)
Ki67	−0.793	0.532	2.222	0.136	0.452(0.159–1.284)
VI	2.165	0.414	27.396	0.000	8.712(3.873–19.595)
PIV	−0.009	0.004	4.726	0.030	0.991(0.984–0.999)
SII	0.012	0.002	28.246	<0.001	1.012(1.008–1.016)
Constant	−5.488	1.179	21.659	<0.001	0.004

Abbreviations: ALN, axillary lymph node; ER, estrogen receptor; PR, estrogen receptor; HER2, human epidermal growth factor receptor2; VI, vascular invasion; SII, platelet × count × neutrophil count/lymphocyte count; PIV, platelet count × neutrophil count × monocytes count/lymphocyte count.

indicate a higher risk of axillary lymph node metastases among breast cancer patients in the present study, which will be valuable for the identification of axillary lymph node metastases in patients with breast cancer.

The status of the ALN is the most important factor in deciding the therapeutic options for patients. Yousif A Kariri found that VI was an independent risk factor for axillary lymph node metastases.[25] Our study also indicated that positive

VI has a higher risk of axillary lymph node metastases compared with negative VI in breast cancer patients. The diagnosis of VI is usually made post-operatively after analysis by pathology. Nevertheless, in our study, it can be detected by blood predictors and used as an auxiliary diagnostic marker to determine axillary lymph node metastases in breast cancer patients, which may have a better application. Furthermore, we also found that higher expression of HER2 was a risk factor for axillary lymph node metastases among breast cancer patients, which was by previous studies.[26,27]

There are some limitations of the research. First, blood indicators may be affected by infection. Second, our study was a single-center, retrospective study in some parts of China. Thus, more prospective multi-center large sample studies are desired to warrant our results. In the future, we will develop a predictive model based on preoperative blood inflammatory indicators (containing SII and PIV) for the postoperative prediction of axillary lymph node metastases in patients with breast cancer to help clinicians conduct an accurate risk assessment for breast cancer patients and to assist a physician in making decisions about the diagnosis of them.

Conclusion

In summary, high levels of SII, PIV, VI and HER2 were the risk factors for axillary lymph node metastases in breast cancer patients.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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