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Original Article

Association between the platelet to lymphocyte ratio, neutrophil to lymphocyte ratio and axillary lymph node metastasis in cT1N0 breast cancer patients

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Abstract: Objective: To investigate the relationship between platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and axillary lymph node metastasis in cT1N0 breast cancer patients. Methods: The clinicopathological data of 154 patients with cT1N0 breast cancer from January 2015 to June 2020 were retrospectively analyzed. All patients underwent sentinel lymph node (SLN) biopsy. The differences of PLR and NLR levels among groups with different clinicopathological factors (age, tumor size, ER, PR, HER-2, Ki67, p53 expression levels, vascular tumor thrombus and SLN metastasis) were compared. The relationship between clinicopathological factors and metastasis of SLN and non-SLN was analyzed. Results: There were 32 patients with SLN metastasis. The cut-off values of PLR and NLR for the whole group were 142.91 and 2.84. The PLR level was higher in patients with vascular tumor thrombus and SLN metastasis (P<0.05), and the NLR level was higher in patients with P53 negative and SLN metastasis groups (P<0.05). According to univariate analysis, there were significant differences in SLN metastasis among different tumor sizes, vascular tumor thrombus states, PLR and NLR levels (P<0.05), but there was no significant difference in SLN metastasis among patients with different ages, ER, PR, HER-2, Ki67, p53 expression groups (P>0.05). According to multivariate analysis, the risk of SLN metastasis in patients with vascular tumor thrombus was higher than that in patients without vascular tumor thrombus (P<0.05). The risk of SLN metastasis in patients with high level of PLR was higher than that in patients with low level of PLR (P<0.05). The difference was not significant in SLN metastasis status among patients with different ages and ER, PR, HER-2, Ki67, p53 expression and NLR level (P>0.05). Conclusion: High level of PLR and vascular tumor thrombus are the risk factors for SLN metastasis.

Keywords: Breast cancer, platelet to lymph node cell ratio, neutrophil to lymphocyte ratio, sentinel lymph node, non-sentinel lymph node

Introduction

Breast cancer is the most common malignant tumor in women, which seriously harms women's physical and mental health [1]. Lymph node metastasis of breast cancer indicates poor prognosis, which has very important clinical significance [2]. Sentinel lymph node biopsy (SLNB) has become a standard surgical procedure for early breast cancer patients with axillary lymph node (ALN) negative on clinical diagnose [3, 4]. SLNB can avoid complications from unnecessary axillary lymph node dissection (ALND). In this paper, axillary lymph nodes (ALN) other than sentinel lymph nodes (SLN) are called non-sentinel lymph nodes (non-SLN). Some studies have shown that in those patients with 1-2 metastatic SLNs, the risk of metastasis in non-SLN is about 28.6% [5]. These patients can be considered to be exempted from ALND [6-8]. Many studies have attempted to find the related factors of SLN and non-SLN metastasis, and some prediction models of metastasis risk have been developed. But most

of the prediction models are based on pathological factors, while only a handful of models involve hematology.

Recent years people found that lymph node metastasis in breast cancer is correlated with inflammatory activation [9], in the meanwhile some studies found that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with a variety of solid tumors such as nasopharyngeal cancer, pancreatic cancer, intestinal cancer and ovarian cancer. There's still a small number of studies conducted on breast cancer. Studies have shown that in patients with stage T1 breast cancer, high level of PLR indicates a high risk of lymph node metastasis [10]. However, it has also been reported that the PLR of patients with non-SLN metastasis is lower than that of patients without non-SLN metastasis [11]. There are still reports of 1-2 SLN-positive stage T1-2 breast cancer patients, and the level of NLR is not related to non-SLN metastasis [12]. This study was intended to conduct a retrospective study on patients with stage cT1N0M0 breast cancer in our hospital, aiming to investigate the predictive value of PLR and NLR on SLN and non-SLN metastasis in breast cancer patients.

Materials and methods

General information

This study included a total of 154 breast cancer patients who underwent SLNB between January 1st, 2015, to June 30, 2020, at The Hospital of Shunyi District Beijing. Clinical data were collected, including age, tumor size, ER, PR, HER-2, Ki67, the level of P53, vessel tumor thrombus and lymph node metastasis. American Joint Committee on Cancer [AJCC] version 8 was used for staging.

Inclusion criteria: 1) patients with invasive breast cancer confirmed by histopathology; 2) patients with no history of chronic disease; 3) patients whose preoperative clinical imaging examination showed T1N0; 4) patients with no distant metastasis.

Exclusion criteria: 1) long term oral administration of aspirin, warfarin, plavix and other anticoagulant drugs; 2) patients with other malignant tumors or hypercoagulable state diseases; 3) patients allergic to methylene blue or nano carbon; 4) patients with preoperative neoadjuvant therapy; 5) patients with axillary surgery history.

This study was approved by the Ethics Committee of The Hospital of Shunyi District Beijing. Informed consent from patients was obtained and forms were signed.

Methods

Fast-fasting peripheral venous blood (2 ml) was collected from all subjects before surgery. The parameters of platelets, lymphocytes and neutrophils were measured by automatic hematology analyzer. PLR was calculated by absolute platelet count divided by absolute lymphocyte count, and NLR was calculated by absolute neutrophil count divided by absolute lymphocytic count. SLNB was traced by the dye method (methylene blue or nano carbon). If SLN metastasis was confirmed by pathology, ALND was performed. Finally, the metastases of SLN and non-SLN were analyzed.

The results of immunohistochemistry were determined as follows: the CUT OFF value of Estrogen Receptor (ER) and Progesterone Receptor (PR) were set as 1%, <1% was negative, and ≥1% was positive [13]. Human epidermal growth factor receptor 2 (HER-2) expression can be divided into 0~+, ++ and +++ according to HER-2 Detection Guidelines for breast cancer (2019 edition) [14]. 0~+ was defined as negative; +++ was defined as positive; If the result was ++, then further FISH test should be performed, and amplified type means positive, unamplified type means negative. The cut-off value of Ki-67 was set as 20%, <20% was low expression, and ≥20% was high expression [15]. p53 was positive when brown particles appeared in the nucleus, and 5 high power fields were randomly selected from each sample. The proportion of positive cells <10% was negative, and ≥10% was positive.

Statistical methods

The data of this study were analyzed by SPSS 21.0 software. PLR and NLR were expressed as mean ± stand divination (x ± sd). According to the status of SLN metastasis, patients were divided into SLN positive group (metastasis) and negative group (non-metastasis). The Receiver operating characteristic (ROC) curve was drawn. PLR and NLR cut-off values were calculated according to the maximum Youden

Table 1. Baseline characteristics of subjects

		Cases	Constituent ratio (%)
Age (year)	≤55	73	47.40
	>55	81	52.60
Tumor size (cm)	≤1	42	27.27
	>1	112	72.73
ER	Negative	50	32.47
	Positive	104	67.53
PR	Negative	71	46.10
	Positive	83	53.90
HER-2	Negative	111	72.08
	Positive	43	27.92
Ki67	Low expression	60	38.96
	High expression	94	61.04
P53	Negative	105	68.18
	Positive	49	31.82
Vascular tumor thrombus	No	131	85.06
	Yes	23	14.94

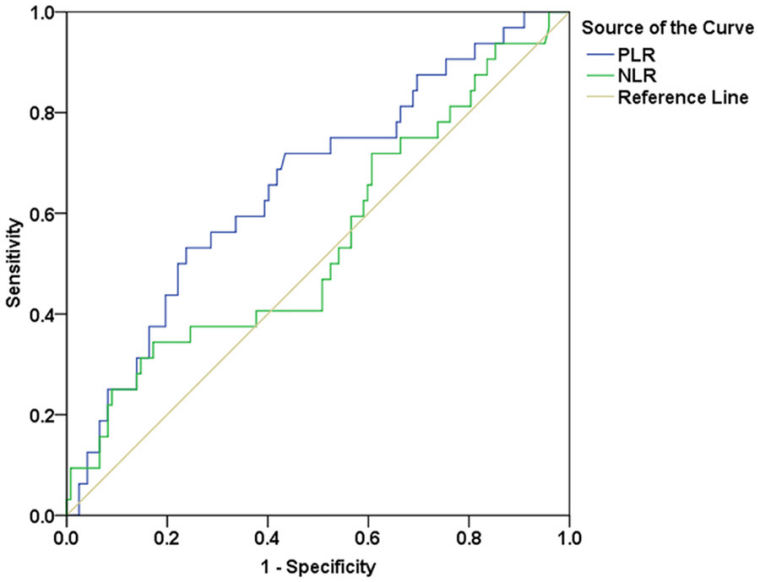

Figure 1. ROC curve of relationship between preoperative PLR, NLR level and SLN metastasis. ROC: Receiver operating characteristic; PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; SLN: sentinel lymph node.

index, and patients were divided into high and low level groups. The differences of PLR and NLR levels among groups with different age, tumor size, ER, PR, HER-2, Ki67, p53 expression levels, vascular tumor thrombus and SLN metastasis were compared by χ^2 test. Logistic regression analysis was used to analyze the relationship between different clinicopathological factors and SLN metastasis. For the SLN positive group, Fisher exact probability method was used to analyze the relationship between different clinicopathological factors and non-SLN metastasis. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients

In this study, 154 patients were included, and the median age was 56 years (range 31-83 years). The basic characteristics of the patients were shown in **Table 1**. Of the 154 patients, 2 underwent breast conserving surgery +SLNB, 120 underwent mastectomy +SLNB, 5 underwent breast conserving surgery +ALND, and 27 underwent mastectomy +ALND because of sentinel lymph node positivity. The median number of SLN detected was 3 (range 2-6).

The relationship between the level of PLR, NLR and different clinicopathological factors

The cut-off values of PLR and NLR: In this study, the mean PLR value and NLR value of patients were 133.41±52.74 and 2.18±1.20; There were two groups based on sentinel lymph node metastatic status, the value were 128.49±52.47 and 2.09±1.03 in the SLN negative group, and 152.18±50.27 and 2.50±1.70 in the SLN positive group. ROC curves were drawn based on the relationship between PLR, NLR and SLN metastasis. The area under the curve was estimated to be 0.685 and 0.548, respectively (**Figure 1**). The PLR and NLR values corresponding to the maximum of Youden index were taken as the cut-off values, and the cut-off values of PLR and NLR were 142.91 and 2.84, respectively.

Table 2. Relationship between PLR, NLR and clinicopathological factors

		PLR		P	NLR		P
		High	Low		High	Low	
Age (year)	≤55	50	23	0.674	56	17	0.466
	>55	58	23		66	15	
Tumor size (cm)	≤1	29	13	0.857	31	11	0.311
	>1	79	33		91	21	
ER	Negative	36	14	0.725	40	10	0.869
	Positive	72	32		82	22	
PR	Negative	46	25	0.180	56	15	0.922
	Positive	62	21		66	17	
HER-2	Negative	76	35	0.469	89	22	0.637
	Positive	32	11		33	10	
Ki67	Low expression	47	13	0.076	52	8	0.069
	High expression	61	33		70	24	
P53	Negative	71	34	0.319	77	28	0.008
	Positive	37	12		45	4	
Vascular tumor thrombus	Negative	96	35	0.041	105	26	0.577*
	Positive	12	11		17	6	
SLN status	Negative	93	29	0.001	101	21	0.033
	Positive	15	17		21	11	

Note: PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; SLN: sentinel lymph node. *which was analyzed by Fisher exact probability method.

The relationship between the levels of PLR and NLR and different clinicopathological factors: According to the cut-off value of PLR and NLR, patients were divided into PLR value high level group (≥142.91) and PLR value low level group (<142.91), NLR value high level group (≥2.84) and NLR value low level group (<2.84). The results (**Table 2**) showed that there were significant differences in PLR levels between the groups with or without vascular tumor thrombus (P=0.041) and between the groups with different SLN metastasis status (P=0.001). However, there was no significant difference in PLR among groups with different ages, tumor sizes and ER statue, PR statue, HER-2 statue, Ki67 and p53 expression levels (all P>0.05). There were significant differences in NLR among groups with different p53 expression (P=0.008) and SLN metastasis (P=0.033). However, there was no significant difference in NLR among groups with different ages, tumor sizes and ER statue, PR statue, HER-2 statue, Ki67 expression and with or without vascular tumor thrombus (P>0.05).

The relationship between SLN, non-SLN metastasis and clinicopathological factors

In our study, there were 32 patients with positive SLN, accounting for 20.78% (32/154). After axillary lymph node dissection of the patients with positive SLN, 12 patients (37.5%, 12/32) were found to have positive non-SLN, and the other 20 patients only had SLN metastasis. Univariate analysis results showed as follows: there were statistically significant differences in SLN metastasis among groups with different tumor sizes, different levels of PLR and NLR, with or without vascular tumor thrombus (P< 0.05), but there was no significant difference in SLN metastasis status among groups with different age, ER statue, PR statue, HER-2 statue, Ki67 and p53 expression (P>0.05) (**Table 3**). The results of multivariate analysis showed that the risk of SLN metastasis in patients with vascular tumor thrombus was higher than that in patients without vascular tumor thrombus (P<0.001; **Table 4**). The risk of SLN metastasis in patients with high level of PLR was higher than that in patients with low level of PLR (P=0.026). However, there was no significant difference in SLN metastasis status among groups with different age, ER statue, PR statue, Her-2 statue, Ki67 expression, p53 expression and NLR value (P>0.05). Clinicopathological factor analysis was performed on 32 patients with positive SLN, and the results showed that there was no statistically significant difference in non-SLN metastatic status among different

Table 3. Relationship between SLN, non-SLN metastasis and clinicopathological factors (univariate analysis)

		SLN Status		χ^2	P	non-SLN status		P
		Negative	Positive			Negative	Positive	
Age (year)	≤50	55	18	1.268	0.260	11	7	1.000
	>50	67	14			9	5	
Tumor size (cm)	≤1	38	4	4.444	0.035	3	1	1.000
	>1	84	28			17	11	
ER	Negative	40	10	0.027	0.869	7	3	0.703
	Positive	82	22			13	9	
PR	Negative	57	14	0.090	0.764	9	5	1.000
	Positive	65	18			11	7	
HER-2	Negative	89	22	0.222	0.637	13	9	0.703
	Positive	33	10			7	3	
Ki67	Low	48	12	0.036	0.849	9	3	0.452
	High	74	20			11	9	
P53	Negative	81	24	0.866	0.352	17	7	0.116
	Positive	41	8			3	5	
Vascular tumor thrombus	No	113	18		<0.001*	13	5	0.277
	Yes	9	14			7	7	
PLR	Low	93	15	10.428	0.001	11	4	0.291
	High	29	17			9	8	
NLR	Low	101	21	4.536	0.033	13	8	1.000
	High	21	11			7	4	

Note: The non-SLN metastasis state was analyzed by Fisher exact probability method. PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; SLN: sentinel lymph node; non-SLN: non-sentinel lymph node. *which was analyzed by Fisher exact probability method.

Table 4. Relationship between SLN and clinicopathological factors (multivariate analysis)

	B	SE	Wals	Sig	Exp (B) (95% CI)
Constant	-4.020	2.099	3.668	0.055	0.018
Age	-0.035	0.023	2.476	0.116	0.965 (0.924-1.009)
Tumor size	1.074	0.644	2.780	0.095	2.927 (0.828-10.343)
ER	-0.044	0.691	0.004	0.116	0.965 (0.924-1.009)
PR	0.533	0.629	0.719	0.396	1.704 (0.497-5.842)
HER-2	0.749	0.547	1.872	0.171	2.114 (0.724-6.176)
Ki67	-0.438	0.533	0.675	0.411	0.645 (0.227-1.835)
P53	-0.448	0.595	0.569	0.451	0.639 (0.199-2.048)
Vascular tumor thrombus	2.167	0.562	14.850	<0.001	8.733 (2.900-26.292)
PLR	1.192	0.537	4.927	0.026	3.293 (1.150-9.434)
NLR	0.436	0.584	0.557	0.455	1.546 (0.492-4.854)

Note: PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio.

clinicopathological factor groups (P>0.05) (**Table 3**).

Discussion

At present, there is no argument that SLNB is the standard procedure for ALN for cT1N0 breast cancer patients, and dye combined isotope double tracer method is recommended for SLN tracer method [3]. However, due to the Limitations of isotope application, most hospitals in China still use the single dye method of methylene blue or nano carbon for tracing. It was reported that the detection rate of SLN

with single methylene blue dye method was only 89.1%, and the failure rate of SLNB was higher in patients who underwent breast-conserving surgery or total mastectomy plus breast reconstruction [16]. It was also reported that the detection rate of SLN with single application of nano carbon was higher than that of single methylene blue group (96.3% vs 92.5%), and the detection rate of SLN could be improved by the addition of indocyanine green combined with methylene blue [17, 18]. However, due to the limitation, our hospital only used the dye method (methylene blue or nano carbon) to locate SLN. The number of patients successfully detected by SLN accounted for 94.48% (154/163) of T1N0 tumor patients who underwent SLNB in the same period, and the median number of SLN biopsies was 3, which was similar to literatures [19]. Preoperative localization of SLN by contrast-enhanced ultrasound improves the detection rate and accuracy of SLN [20]. Our hospital has also actively explored this issue. In this study, 15 cases of SLN were located by contrast-enhanced ultrasound before operation and SLN was successfully detected. Among them, blue stained SLN and SLN were not found in the traditional axillary incision of one patient. After total mastectomy, the blue stained SLN was found in the deep side of coracoclavicular fascia, which was close to the surface location of ultrasound imaging.

It was reported that the SLN metastasis rate of T1 invasive breast cancer was about 18.3%-21.1% [10, 19]. The positive rate of SLN in patients with a tumor larger than 1 cm was higher than that in patients with tumor size less than or equal to 1 cm, while in patients with positive SLN, the metastasis rate of non-SLN was 27.8%-38.9% [10, 19, 21, 22]. In this study, the SLN metastasis rate was 20.78% (32/154). Patients were divided into two groups according to tumor size: the tumor size >1 cm and the tumor size ≤1 cm. The SLN metastasis rates of the two groups were 25% (28/112) and 9.52% (4/42), respectively. The metastasis rates of non-SLN were 39.29% (11/28) and 25% (1/4) respectively. However, the difference between groups with different tumor size was not statistically significant, which may due to the small sample size. Further analysis will be conducted.

There is a lot of research exploring the risk factors of SLN metastasis in breast cancer. Some scholars believe that the risk factor of SLN metastasis is associated with vascular tumor thrombus [19]. This study also confirmed that the risk of SLN metastasis in patients with vascular tumor thrombus is higher than that in patients without vascular tumor thrombus. Meta-analysis showed that level of PLR in patients with ALN metastasis was higher than that in patients without ALN metastasis, and high level of PLR predicted poor disease-free survival (DFS) as well as overall survival (OS) [23-25], and studies have shown that patients with T1 breast cancer with high level of PLR have a higher risk of SLN metastasis than those with low level of PLR [10]. Although Chi et al. reported that TNM stage of patients with high level of NLR was higher than that of patients with low level of NLR, and the risk of ALN metastasis in patients with high level of NLR was higher than that of patients with low level of NLR, the difference was not statistically significant. In this study, the incidence of high level of PLR in the SLN positive group was significantly higher than that in the SLN negative group, which also confirmed that high level of PLR and NLR were related to poor prognosis of breast cancer patients [26]. The relationship between PLR, NLR and SLN metastasis was analyzed. The results showed that high level of PLR was a risk factor for SLN metastasis. Although SLN metastasis rate in the high level of NLR group was higher than that in the lower group according to univariate analysis, it did not show statistical significance in multivariate analysis. It is still necessary to increase the sample size in the follow-up study.

The ACOSOG Z0011 study showed that breast cancer patients with 1-2 SLN positive could be exempted from ALND [6], meanwhile the IBCSG 23-01 study explored that patients with one or more SLN micrometastases did not benefit from ALND over 10 years of follow-up [7]. Because subsequent lymph node metastasis may not occur in all patients with positive SLN, many scholars have explored the non-SLN metastasis prediction model of SLN positive patients. Studies have shown that the occurrence of vascular tumor thrombus and the ratio of SLN positive number/biopsy number >0.5 indicate an increased risk of non-SLN metastasis [19]. Other scholars have reported that vascular invasion, HER-2 overexpression and SLN extracapsular invasion indicate an increased risk of non-SLN metastasis [27]. It was believed that

high level of Ki67 and high amount of SLN are risk factors for non-SLN metastasis [28]. It was reported that vascular tumor thrombus and axillary fat tumor cell deposition predict the risk of 4 or more non-SLN metastasis [29]. However, the above studies very few involved blood inflammatory markers. In this study, the preoperative hematological results of the SLN positive group were analyzed, and non-SLN metastasis in groups with high and low level of PLR and NLR were compared. However, only 32 SLN positive patients were enrolled in the study. Through descriptive analysis, it can be seen that the risk of non-SLN metastasis in the group with a high level of PLR is higher than that in the group with a low level of PLR, and there is no significant difference in the risk of non-SLN metastasis among groups with different levels of NLR. Although no positive results were obtained by comparative analysis, it may be considered that results with a statistical difference may be obtained when the sample size is increased.

In conclusion, high level of PLR and vascular tumor thrombus were the risk factors of SLN metastasis. For SLN positive patients, the relationship between high level of PLR and non-SLN metastasis needed a further research.

Disclosure of conflict of interest

None.

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