International Journal of General Medicine

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ORIGINAL RESEARCH

The Association of Pretreatment Systemic Immune Inflammatory Response Index (SII) and Neutrophil-to-Lymphocyte Ratio (NLR) with Lymph Node Metastasis in Patients with Papillary Thyroid Carcinoma

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Objective: Immunoinflammatory response can participate in the development of cancer. To investigate the relationship between pretreatment systemic immune inflammatory response index (SII), systemic inflammatory response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and lymph node metastasis in patients with papillary thyroid carcinoma (PTC).

Methods: A retrospective analysis was performed on 547 PTC patients treated in Meizhou People's Hospital from January 2018 to December 2021. Clinicopathological data were collected, including gender, age, Hashimoto's thyroiditis, maximum tumor diameter, extra-membrane infiltration, disease stage, *BRAF* V600E mutation, pretreatment inflammatory index levels, and lymph node metastasis. The optimal cutoff values of SII, SIRI, NLR, PLR and LMR were calculated by receiver operating characteristic (ROC) curve, and the relationship between inflammatory indexes and other clinicopathological features and lymph node metastasis was analyzed.

Results: There were 303 (55.4%) PTC patients with lymph node metastasis. The levels of SII, SIRI, NLR, and PLR in patients with lymph node metastasis were significantly higher than those in patients without lymph node metastasis, while the levels of LMR were significantly lower than those in patients without lymph node metastasis (all $p<0.05$). When lymph node metastasis was taken as the endpoint, the critical value of SII was 625.375, the SIRI cutoff value was 0.705, the NLR cutoff value was 1.915 (all area under the ROC curve >0.6). The results of regression logistic analysis showed that age <55 years old (OR: 1.626, 95% CI: 1.009–2.623, $p=0.046$), maximum tumor diameter >1cm (OR: 2.681, 95% CI: 1.819–3.952, $p<0.001$), *BRAF* V600E mutation (OR: 2.709, 95% CI: 1.542–4.759, $p=0.001$), SII positive (≥625.375/<625.375, OR: 2.663, 95% CI: 1.560–4.546, $p<0.001$), and NLR positive (≥1.915/<1.915, OR: 1.808, 95% CI: 1.118–2.923, $p=0.016$) were independent risk factors for lymph node metastasis of PTC.

Conclusion: Age <55 years old, maximum tumor diameter >1cm, *BRAF* V600E mutation, SII positive, and NLR positive were independent risk factors for lymph node metastasis in PTC.

Keywords: papillary thyroid carcinoma, lymph node metastasis, systemic immune inflammatory response index, systemic inflammatory response index, neutrophil-to-lymphocyte ratio

Introduction

Thyroid cancer is the most common malignant tumor of the endocrine system and one of the most common malignant tumors of the head and neck.[1,2] Over the past few decades, the incidence of thyroid cancer has shown an overall increase worldwide.[3] In recent years, the incidence and mortality of thyroid cancer have increased in China.[4] With the aging of the population, the burden of thyroid cancer in China will become more and more serious.[5] According to pathological

Received: 27 January 2024
Accepted: 18 June 2024
Published: 1 July 2024

classification, most thyroid cancers are differentiated thyroid cancers, including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), and PTC accounts for about 80% of thyroid malignancies.[6]

PTC originates from thyroid follicular epithelial cells and is the most common histopathological type of thyroid cancer.[7] Postoperative pathological examination showed that 20%-50% of PTC patients had lymph node metastasis.[8,9] The presence of lymph node metastasis not only affects the prognosis of patients, but also increases the postoperative recurrence rate and mortality.[10] About 15% of cases with lymph node metastasis exhibit aggressive tumor behavior, which is reflected in regional invasion, distant metastasis, treatment tolerance, and increased mortality.[11] There are abundant lymph nodes in the human neck, and the lymph nodes around the thyroid gland are connected with the lymphatic vessels in the neck, which may be one of the reasons why PTC is prone to lymph node metastasis.[12] Whether prophylactic lymph node dissection is appropriate for all patients with surgically treated thyroid cancer is controversial: prophylactic lymph node dissection may result in hypoparathyroidism in patients without lymph node metastasis, while metastatic lymph nodes may be present in patients without lymph node dissection.[13] Both imaging methods and laboratory techniques are deeply exploring the markers, diagnostic accuracy and mechanism of lymph node metastasis in thyroid cancer.[14,15] Therefore, the factors affecting lymph node metastasis of thyroid cancer need to be explored and studied continuously.

The immune inflammatory response is involved in the development and progression of many diseases.[16,17] Immunoinflammatory response can participate in the development of cancer.[18,19] Systemic immune inflammation index (SII) and system inflammation response index (SIRI) are two markers of systemic immune inflammation, and their links to a number of diseases are being revealed.[20–22] SII is a comprehensive indicator that combines neutrophils, platelets and lymphocytes, and has been proven to predict the prognosis of various cancers such as hepatocellular carcinoma, pancreatic cancer, and cervical cancer.[23,24] The SIRI index is a comprehensive index combining lymphocytes, monocytes and neutrophils, which has been confirmed to be related to the prognosis of pancreatic cancer, gastric cancer and breast cancer.[25–27] In addition, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been found to be associated with the progression of cancer.[28–30] However, the relationship between these immunoinflammatory markers and lymph node metastasis in PTC remains unclear. This study evaluated the relationship between these immunoinflammatory markers and lymph node metastasis in patients with PTC.

Materials and Methods

Subjects

It was a retrospective study with a total of 547 patients with PTC who were hospitalized in Meizhou People's Hospital, from January 2018 to December 2021. Inclusion criteria: (1) All PTC patients were confirmed by histopathology and imaging examination; (2) Complete records of medical records received in our hospital for diagnosis and treatment; (3) There was at least one peripheral blood cell analysis record in our hospital before the start of treatment. Exclusion criteria: (1) Previous history of other malignant tumor diseases; (2) Pathological types other than papillary thyroid carcinoma; (3) Patients with dysfunction of important organs. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Data Collection

Clinicopathological features of the patients were collected from the medical records system of our hospital, including gender, age, Hashimoto's thyroiditis, maximum tumor diameter, extra-membrane infiltration, disease stage, and lymph node metastasis. Blood routine test data were collected at admission and 2–3 days before treatment. The blood routine test was to collect 2mL of the patient's blood sample through via venipuncture of an antecubital vein, which was collected in a test tube with ethylenediamine tetraacetic acid (EDTA) as an anticoagulant, and tested by Sysmex XE-2100 hematology analyzer (Sysmex Corporation, Japan) according to standard operating procedures (SOP). The results of *BRAF* gene mutation detection in tumor tissue of patients were collected. *BRAF* V600E mutation was detected by real-time amplification refractory mutation system (ARMS)-PCR as previously described.[31]

Data Processing and Statistical Analysis

The inflammation index SII, SIRI, NLR, PLR and LMR were calculated according to the following formula:

SII=platelet×neutrophil/lymphocyte

SIRI=monocyte×neutrophil/lymphocyte

NLR=neutrophil/lymphocyte

PLR=platelet/lymphocyte

LMR= lymphocyte/monocyte.

SPSS statistical software version 26.0 (IBM Inc., USA) was used for data analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of SII, SIRI, NLR, PLR, and LMR to distinguish lymph node metastasis. Association between lymph node metastasis and the clinicopathological features of PTC patients was evaluated by *Chi*-square test or Fisher's exact test. Logistic regression analysis was used to evaluate the relationship between these inflammatory markers, clinicopathological features and lymph node metastasis in PTC patients. $p<0.05$ was set as statistically significant.

Results

Clinicopathological Features of PTC Patients

Of the 547 patients included in the study, 82 (15.0%) were male and 465 (85.0%) were female; there were 443 cases (81.0%) were younger than 55 years old and 104 cases (19.0%) were ≥55 years old, indicating that the majority of PTC patients were young women. There were 70 (12.8%) PTC patients with Hashimoto's thyroiditis. There were 257 (47.0%) cases and 47 (8.6%) cases with the maximum tumor diameter >1cm and extra-membrane infiltration, respectively. There were 303 (55.4%), 6 (1.1%), and 472 (86.3%) PTC patients with lymph node metastasis, distant metastasis, and *BRAF* V600E mutation, respectively. The levels of SII, SIRI, NLR, PLR, and LMR in these patients were 480.15 (345.29, 664.44), 0.78 (0.54, 1.18), 1.90 (1.47, 2.45), 127.40 (101.82, 160.00), and 4.76±1.74, respectively (Table 1).

Table 1 The Clinicopathological Features of PTC Patients

Clinicopathological Features	PTC Patients (n=547)
Gender	
Male, n (%)	82 (15.0%)
Female, n (%)	465 (85.0%)
Age (Years)	
<55, n (%)	443 (81.0%)
≥55, n (%)	104 (19.0%)
Hashimoto's thyroiditis	
No, n (%)	477 (87.2%)
Yes, n (%)	70 (12.8%)
Maximum tumor diameter	
≤1cm, n (%)	290 (53.0%)
>1cm, n (%)	257 (47.0%)
Extra-membrane infiltration	
No, n (%)	500 (91.4%)
Yes, n (%)	47 (8.6%)
TNM stage	
I-II, n (%)	499 (91.2%)
III-IV, n (%)	48 (8.8%)
Lymph node metastasis	
No, n (%)	244 (44.6%)
Yes, n (%)	303 (55.4%)

(*Continued*)

Table 1 (Continued).

Clinicopathological Features	PTC Patients (n=547)
Distant metastasis	
No, n (%)	541 (98.9%)
Yes, n (%)	6 (1.1%)
BRAF V600E mutation	
No, n (%)	75 (13.7%)
Yes, n (%)	472 (86.3%)
Inflammation index levels	
SII, median (P25, P75)	480.15 (345.29, 664.44)
SIRI, median (P25, P75)	0.78 (0.54, 1.18)
NLR, median (P25, P75)	1.90 (1.47, 2.45)
PLR, median (P25, P75)	127.40 (101.82, 160.00)
LMR, means±SD	4.76±1.74

Abbreviations: SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; p25, 25th percentile; p75, 75th percentile.

Comparison of Clinicopathological Features Among PTC Patients with or Without Lymph Node Metastasis

In this study, 244 PTC patients (44.6%) had no lymph node metastasis and 303 PTC patients (55.4%) with lymph node metastasis. The proportion of PTC patients with lymph node metastasis who were younger than 55 years old (84.2% vs 77.0%, p=0.038), maximum tumor diameter >1cm (58.4% vs 32.8%, p<0.001), with extra-membrane infiltration (11.2% vs 5.3%, p=0.020), and with *BRAF* V600E mutation (89.1% vs 82.8%, p=0.034) was higher than that of PTC patients without lymph node metastasis, respectively. The levels of SII, SIRI, NLR, and PLR in patients with lymph node metastasis were significantly higher than those in patients without lymph node metastasis, while the levels of LMR were significantly lower than those in patients without lymph node metastasis (all p<0.05). There were no statistically significant differences in gender distribution and proportion of Hashimoto's thyroiditis patients between those with and without lymph node metastasis (Table 2).

Table 2 Comparison of Clinicopathological Features Among PTC Patients with or Without Lymph Node Metastasis

Clinicopathological Features	Lymph Node Metastasis		*p* values
	No (n=244)	Yes (n=303)	
Gender			
Male, n (%)	31(12.7%)	51(16.8%)	0.187
Female, n (%)	213(87.3%)	252(83.2%)	
Age (Years)			
<55, n (%)	188(77.0%)	255(84.2%)	0.038
≥55, n (%)	56(23.0%)	48(15.8%)	
Hashimoto's thyroiditis			
No, n (%)	214(87.7%)	263(86.8%)	0.798
Yes, n (%)	30(12.3%)	40(13.2%)	
Maximum tumor diameter			
≤1cm, n (%)	164(67.2%)	126(41.6%)	<0.001
>1cm, n (%)	80(32.8%)	177(58.4%)	
Extra-membrane infiltration			
No, n (%)	231(94.7%)	269(88.8%)	0.020
Yes, n (%)	13(5.3%)	34(11.2%)	

(*Continued*)

Table 2 (Continued).

Clinicopathological Features	Lymph Node Metastasis		*p* values
	No (n=244)	Yes (n=303)	
BRAF V600E mutation			
No, n (%)	42(17.2%)	33(10.9%)	0.034
Yes, n (%)	202(82.8%)	270(89.1%)	
Inflammation index levels			
SII, median (P25, P75)	425.23 (320.88, 573.23)	525.35 (381.77, 751.30)	<0.001
SIRI, median (P25, P75)	0.69 (0.51, 1.00)	0.86 (0.61, 1.43)	<0.001
NLR, median (P25, P75)	1.72 (1.36, 2.20)	2.06 (1.63, 2.79)	<0.001
PLR, median (P25, P75)	122.06 (98.02, 152.00)	133.33 (105.00, 171.63)	0.001
LMR, means±SD	5.05±1.63	4.53±1.80	0.001

Abbreviations: SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; p25, 25th percentile; p75, 75th percentile.

The Clinicopathological Features of PTC Patients Were Compared According to the Levels of Inflammation Indexes

ROC curve analysis was used to determine the optimal cutoff values of SII, SIRI, NLR, PLR, and LMR to distinguish lymph node metastasis. When lymph node metastasis was taken as the endpoint of SII, SIRI, NLR, PLR, and LMR, the critical value of SII was 625.375 (sensitivity 39.9%, specificity 84.4%, area under the ROC curve: 0.644), the SIRI cutoff value was 0.705 (sensitivity 65.0%, specificity 52.0%, area under the ROC curve: 0.625), the NLR cutoff value was 1.915 (sensitivity 60.4%, specificity 64.3%, area under the ROC curve: 0.653), the PLR cutoff value was 124.165 (sensitivity 58.4%, specificity 52.9%, area under the ROC curve: 0.583), and the LMR cutoff value was 4.615 (sensitivity 55.4%, specificity 55.7%, area under the ROC curve: 0.582). We selected those with an area under the ROC curve >0.6 as valuable candidate markers for lymph node metastasis (Figure 1).

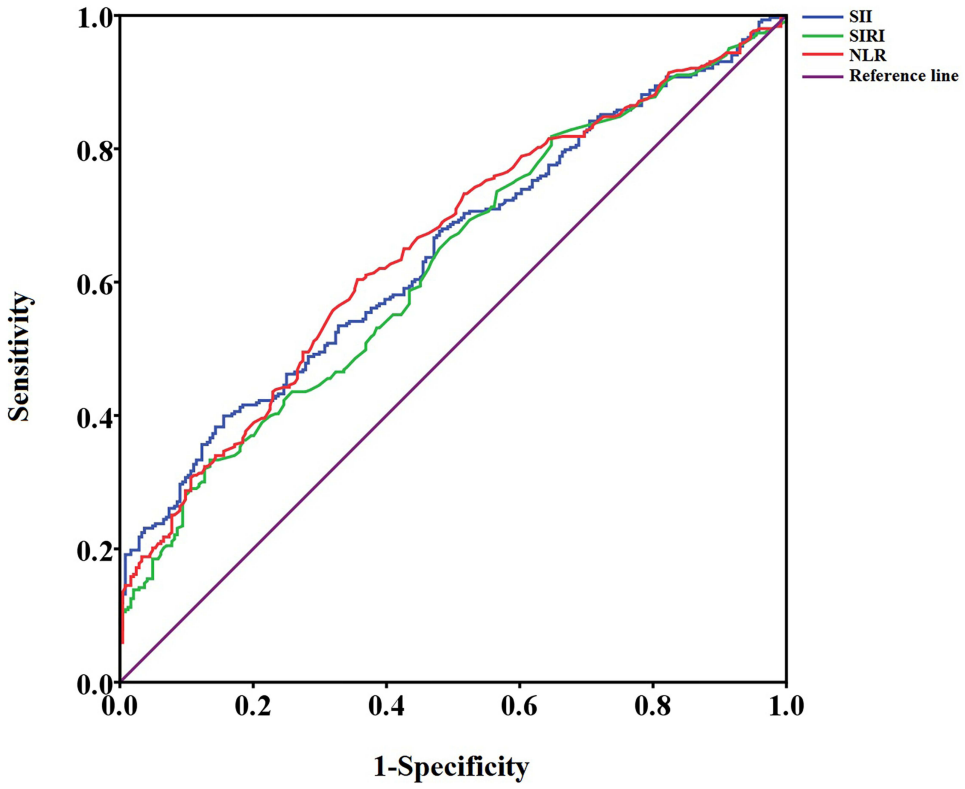

Figure 1 The ROC curve of SII, SIRI, and NLR based on the lymph node metastasis.

The proportion of patients with maximum tumor diameter >1cm and TNM stage III-IV in SII, SIRI and NLR positive patients was higher than that in SII, SIRI and NLR negative patients, respectively (all $p<0.05$). The proportion of *BRAF* V600E mutations was higher in SII negative (<625.375) patients than in SII positive (≥625.375) patients (89.2% vs 79.2%, $p=0.003$). There were no significant differences in gender distribution, age distribution, proportion of Hashimoto's thyroiditis, and proportion of extradadenial invasion among different expression levels of SII, SIRI and NLR (Table 3).

Logistic Regression Analysis of Risk Factors of Lymph Node Metastasis of PTC

Univariate analysis and multivariate regression logistic analysis were performed to measure the relationship between the clinicopathological features and lymph node metastasis. The Results of univariate analysis showed that age <55 years old (odds ratio (OR): 1.582, 95% confidence interval (CI): 1.030–2.430, $p=0.036$), maximum tumor diameter >1cm (OR: 2.880, 95% CI: 2.026–4.093, $p<0.001$), extra-membrane infiltration (yes vs no, OR: 2.246, 95% CI: 1.157–4.358, $p=0.017$), *BRAF* V600E mutation (OR: 1.701, 95% CI: 1.041–2.780, $p=0.034$), SII positive (≥625.375/<625.375, OR: 3.604, 95% CI: 2.379–5.460, $p<0.001$), SIRI positive (≥0.705/<0.705, OR: 2.017, 95% CI: 1.429–2.848, $p<0.001$), and NLR positive (≥1.915/<1.915, OR: 2.752, 95% CI: 1.942–3.900, $p<0.001$) were significantly associated with lymph node metastasis. Multivariate regression logistic analysis showed that age <55 years old (OR: 1.626, 95% CI: 1.009–2.623, $p=0.046$), maximum tumor diameter >1cm (OR: 2.681, 95% CI: 1.819–3.952, $p<0.001$), *BRAF* V600E mutation (OR: 2.709, 95% CI: 1.542–4.759, $p=0.001$), SII positive (≥625.375/<625.375, OR: 2.663, 95% CI: 1.560–4.546, $p<0.001$), and NLR positive (≥1.915/<1.915, OR: 1.808, 95% CI: 1.118–2.923, $p=0.016$) were independent risk factors for lymph node metastasis of PTC (Table 4).

Table 3 The Clinicopathological Features of PTC Patients Were Compared According to the Expression Levels of SII, SIRI and NLR

Clinicopathological Features	SII		*p* values	SIRI		*p* values	NLR		*p* values
	<625.375 (n=388)	≥625.375 (n=159)		<0.705 (n=233)	≥0.705 (n=314)		<1.915 (n=277)	≥1.915 (n=270)	
Gender									
Male, n (%)	59(15.2%)	23(14.5%)	0.895	29(12.4%)	53(16.9%)	0.183	44(15.9%)	38(14.1%)	0.632
Female, n (%)	329(84.8%)	136(85.5%)		204(87.6%)	261(83.1%)		233(84.1%)	232(85.9%)	
Age (Years)									
<55, n (%)	308(79.4%)	135(84.9%)	0.151	186(79.8%)	257(81.8%)	0.582	221(79.8%)	222(82.2%)	0.514
≥55, n (%)	80(20.6%)	24(15.1%)		47(20.2%)	57(18.2%)		56(20.2%)	48(17.8%)	
Hashimoto's thyroiditis									
No, n (%)	342(88.1%)	135(84.9%)	0.325	204(87.6%)	273(86.9%)	0.897	246(88.8%)	231(85.6%)	0.306
Yes, n (%)	46(11.9%)	24(15.1%)		29(12.4%)	41(13.1%)		31(11.2%)	39(14.4%)	
Maximum tumor diameter									
≤1cm, n (%)	225(58.0%)	65(40.9%)	<0.001	146(62.7%)	144(45.9%)	<0.001	166(59.9%)	124(45.9%)	0.001
>1cm, n (%)	163(42.0%)	94(59.1%)		87(37.3%)	170(54.1%)		111(40.1%)	146(54.1%)	
Extra-membrane infiltration									
No, n (%)	358(92.3%)	142(89.3%)	0.313	219(94.0%)	281(89.5%)	0.066	259(93.5%)	241(89.3%)	0.093
Yes, n (%)	30(7.7%)	17(10.7%)		14(6.0%)	33(10.5%)		18(6.5%)	29(10.7%)	
TNM stage									
I-II, n (%)	366(94.3%)	133(83.6%)	<0.001	221(94.8%)	278(88.5%)	0.014	263(94.9%)	236(87.4%)	0.002
III-IV, n (%)	22(5.7%)	26(16.4%)		12(5.2%)	36(11.5%)		14(5.1%)	34(12.6%)	
BRAF V600E mutation									
No, n (%)	42(10.8%)	33(20.8%)	0.003	25(10.7%)	50(15.9%)	0.102	30(10.8%)	45(16.7%)	0.062
Yes, n (%)	346(89.2%)	126(79.2%)		208(89.3%)	264(84.1%)		247(89.2%)	225(83.3%)	

Table 4 Logistic Regression Analysis of Risk Factors of Lymph Node Metastasis of PTC

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender (Female/Male)	0.719 (0.444–1.165)	0.180	0.637 (0.374–1.084)	0.097
Age (<55/≥55, years old)	1.582 (1.030–2.430)	0.036	1.626 (1.009–2.623)	0.046
Hashimoto's thyroiditis (Yes/No)	1.085 (0.654–1.801)	0.753	1.091 (0.622–1.914)	0.761
Maximum tumor diameter (>1cm/≤1cm)	2.880 (2.026–4.093)	<0.001	2.681 (1.819–3.952)	<0.001
Extra-membrane infiltration (Yes/No)	2.246 (1.157–4.358)	0.017	1.363 (0.657–2.824)	0.405
BRAF V600E mutation (Yes/No)	1.701 (1.041–2.780)	0.034	2.709 (1.542–4.759)	0.001
SII (≥625.375/<625.375)	3.604 (2.379–5.460)	<0.001	2.663 (1.560–4.546)	<0.001
SIRI (≥0.705/<0.705)	2.017 (1.429–2.848)	<0.001	0.893 (0.568–1.405)	0.625
NLR (≥1.915/<1.915)	2.752 (1.942–3.900)	<0.001	1.808 (1.118–2.923)	0.016

Abbreviations: OR, odds ratio; CI, confidence interval.

Discussion

Immunoinflammatory response can participate in the development of cancer by promoting the proliferation of tumor cells, changing gene homeostasis, inducing invasion and metastasis.[18,19] The inflammatory index has been identified as a novel tumor marker based on host inflammatory response.[32] Lymphocytes and platelets have been proven to promote tumor development, and there is evidence that neutrophils can increase the ability of cancer cell invasion, proliferation, and metastasis, and help cancer cells evade immune surveillance.[33] The increase of monocyte count is associated with the progression of malignant tumors and can reduce the overall survival rate of malignant tumors.[34,35] These results suggest that SII, SIRI and NLR may be closely related to the development of tumors.

Pretreatment SII levels in PTC patients can be used to distinguish benign and malignant thyroid diseases.[36] Tang et al developed a prediction model based on SII and LMR to distinguish PTC from benign thyroid nodules before surgery.[37] Similarly, Deniz MS showed that the NLR and PLR of PTC patients were significantly higher than those of benign thyroid nodules.[38] Zhao et al found that tumor diameter and preoperative SII were independent risk factors for identifying lateral lymph node metastasis (LLNM) based on a study of 713 PTC patients.[39] Zhang et al have shown that SII can effectively predict central lymph node metastasis (CLNM) based on a study of 406 PTC patients.[40] Pang et al found that a higher SIRI (≥0.77) was an independent positive predictor of CLNM in (1394) patients with T1-T2 PTC.[41] However, another study showing that SIRI has no significant difference in inflammation indicators between PTC patients and patients with benign thyroid nodules.[38] In addition, Xie et al found that patients with low SIRI had a higher *BRAF* mutation rate than patients with high SIRI.[42] In this study, patients with low SII had a higher *BRAF* mutation rate than patients with high SII, and no similar results were found in the SIRI classification comparison. The results of this study are different from those of the above studies. It may be related to the difference in the number of studies included and the cutoff values of inflammatory indicators in different studies.

Manatakis et al found that NLR was significantly increased in patients with lymph node positive thyroid tumors.[43] High preoperative NLR is an independent predictor of CLNM based on the analysis in 456 patients with PTC and type 2 diabetes.[44] The NLR of thyroid cancer patients with lateral lymph node metastasis was significantly higher than that of thyroid cancer patients without lateral lymph node metastasis.[45] Shrestha et al found that elevated NLR and PLR were associated with lymph node metastasis in PTC patients.[46] NLR and PLR have predictive value for TNM stage in PTC patients, but the predictive effect is limited.[47] A retrospective analysis of 161 patients with PTC showed that ≥45 years of age, preoperative elevation of NLR is associated with the progression of lymph node metastasis.[48] There are also some studies on the relationship between other immunoinflammatory markers and lymph node metastasis in PTC patients. Kim et al revealed that preoperative high PLR was significantly associated with lateral lymph node metastasis based on the analysis of 1066 female PTC patients.[49] Li et al found no correlation between LMR, PLR and lymph node metastasis in 212 PTC patients.[50] In this study, ROC curve analysis results showed that PLR and LMR were not very good in predicting lymph node metastasis in PTC patients (area under ROC curve was less than 0.6).

The progression of cancer depends to a large extent on the invasion of tumor blood vessels and immune cells.[51] (1) The density of lymphocytes in thyroid lymph node metastases increased, suggesting that lymph node metastases were rich in activated immune cells.[52] (2) Monocytes can penetrate tumor mass, reduce angiogenesis and induce apoptosis of cancer cells, thus reducing tumor invasion and progression, and are important anti-tumor mediators.[53] (3) There is interaction between tumor cells and platelets. Tumor cells can damage the vascular endothelium, thus activating platelets and initiating the coagulation system, causing serious complications such as thrombosis and bleeding. The tripartite interaction between platelets, blood vessel wall, and tumor cells prompts tumor cells to adhere to the blood vessel wall.[54] In addition, myelodysplasia is active in patients with malignant tumors, and tumor cells produce thrombopoietic factors.[54] (4) Neutrophils play various roles in tumor development: synthesizing and releasing a variety of cytokines, promoting angiogenesis, extracellular matrix remodeling, immunosuppression, and further promoting metastasis.[55,56] In general, the tumor microenvironment composed of the above cells is in a relatively stable state, and once the above homeostatic state is broken, tumor cell immune escape and cancer progression may occur.

SII, SIRI and NLR have the advantages of high accessibility, almost non-invasive, low cost and good reproducibility. Similar to classical tumor markers, SII, SIRI and NLR can change with the changes of tumor load and immune inflammatory response status of patients, and this dynamic change can accurately reflect the trend of tumor progression and treatment effect. Therefore, SII, SIRI, and NLR are likely to be good indicators and tools for monitoring systemic immune inflammatory response and predicting changes in cancer patients' characteristics.

In addition, this study also found that maximum tumor diameter > 1cm was an independent risk factor for lymph node metastasis, which may be because malignant nodules with larger diameter were associated with larger perithyroid contact surface, leading to greater risk of cancer cells infiltrating peripheral lymphatic vessels.[57] *BRAF* V600E mutation is considered to be one of the important molecular markers of thyroid cancer progression and prognosis.[58,59] Several studies have shown that *BRAF* V600E mutation is associated with tumor aggressiveness.[31,60] Age <55 years old was a risk factor for lymph node metastasis in PTC in this study. The relationship between age and the risk of lymph node metastasis of thyroid cancer is still more controversial than price, and it is still a question that needs to be explored.[61–63]

This study is one of the few to investigate the relationship between levels of peripheral blood immunoinflammatory markers and lymph node metastasis in patients with PTC. Of course, this study still has the following limitations: (1) This study was a single-center retrospective study, and the study design may lead to bias and incompleteness in data interpretation. (2) This study did not subdivide the types of lymph node metastasis (such as central lymph node metastasis, cervical lymph node metastasis, mediastinal lymph node metastasis, and so on); (3) The study did not cover the dynamic changes of inflammatory markers measured repeatedly at different time points, and the relationship between dynamic changes and lymph node metastasis.

Conclusions

In summary, PTC patients are mostly young women, and more than half of PTC patients have lymph node metastasis. Age (<55 years old), maximum tumor diameter >1cm, *BRAF* V600E mutation, SII positive (≥625.375), and NLR positive (≥1.915) were independent risk factors for lymph node metastasis in PTC.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital. All participants signed informed consent in accordance with the Declaration of Helsinki.

Acknowledgments

The author would like to thank other colleagues whom were not listed in the authorship of Department of Thyroid Surgery, Meizhou People's Hospital for their helpful comments on the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Science and Technology Program of Meizhou (Grant No.: 2019B0202001).

Disclosure

The authors declare that they have no competing interests in this work.

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