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Analysis of the Relationship between Pan-immune-inflammation Value and the Clinical Pathological Characteristics and Surgical Prognosis of Thyroid Cancer

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ABSTRACT

This study aimed to explore the relationship between the preoperative pan-immune-inflammation value (PIV) and the clinicopathological characteristics and surgical prognosis of thyroid cancer.

This retrospective cohort study included 165 patients with thyroid cancer who underwent surgery. The value and clinical applicability of PIV and other immune-inflammatory biomarkers in assessing disease-free survival (DFS) were compared based on the area under the receiver operating characteristic (ROC) curve (AUC) and decision curve analysis (DCA). Patients were divided into high and low PIV groups according to the optimal cutoff value to assess the correlation between PIV and pathological characteristics. The Kaplan-Meier method was used for DFS analysis, and a Cox proportional hazards model was used to analyze the factors affecting DFS.

The AUC of PIV for predicting DFS was higher than that of other immune-inflammatory biomarkers, and PIV demonstrated the highest clinical utility. Compared with the low PIV group, the high PIV group had a lower proportion of papillary thyroid carcinoma, a higher proportion of anaplastic thyroid carcinoma, and higher rates of stage III–IV disease, lymph node metastasis, maximum tumor diameter ≥2 cm, and multiple lesions. The DFS was significantly shorter in the high PIV group than in the low PIV group. After adjusting for confounding factors, a high PIV level was an independent risk factor for poor surgical outcomes.

In conclusion, preoperative PIV is associated with the pathological type of thyroid cancer, TNM stage, lymph node metastasis status, and maximum tumor diameter. Furthermore, a high PIV level can increase the risk of poor surgical outcomes.

Keywords: Pan-immune-inflammation value; Pathological characteristics; Prognosis; Relationship; Thyroid neoplasms.

INTRODUCTION

Thyroid cancer is a common malignant tumor of the endocrine system, originating from epithelial cells of the thyroid gland. Epidemiological statistics show that globally, there were approximately 586,000 new cases of thyroid cancer and 41,100 deaths in 2020, accounting for 3.1% of the total number of new cancer cases, ranking 9th among all types of cancer.[1] Data from the

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IARC 2022 Global Cancer Report show that the number of new thyroid cancer cases in China has exceeded 460,000, accounting for more than half of the global new cases, and the number of deaths accounts for 24.3%.[2] At present, thyroid cancer is primarily treated in the clinic through surgical resection, supplemented by endocrine therapy and radioactive iodine treatment. Although the majority of patients with thyroid cancer have a good prognosis after surgery, some patients still experience recurrence, metastasis, or even death.[3] Thyroid cancer is usually diagnosed through fine-needle aspiration biopsy guided by ultrasound and cytological examination. However, due to the limited sample size and the difficulty in fully identifying follicular lesions, this method has obvious limitations. With the rapid development of high-throughput molecular biology technologies, novel immune biomarkers such as *azurocidin 1* (*AZU1*), *gap junction protein-gamma 1* (*GJC1*), and *C-X-C motif chemokine ligand 5* (*CXCL5*) have been shown to be associated with the occurrence, development, and prognosis of thyroid cancer.[4-6] Although these novel immune biomarkers (such as *AZU1*, *GJC1*, and *CXCL5*) have provided a new perspective for the diagnosis and prognostic assessment of thyroid cancer, their detection often relies on tissue specimens or complex molecular biology techniques, making it difficult to promote their use in primary healthcare institutions. In recent years, some peripheral blood immune-inflammatory indices have also been proven to be associated with the occurrence, development, and prognosis of malignant tumors. In comparison, peripheral blood immune-inflammatory indices have the advantages of convenient detection and low cost, making them more suitable as routine clinical monitoring tools. Peripheral blood immune-inflammatory indices such as lymphocytes, platelets, monocytes, and neutrophils can reflect a patient's immune and inflammatory status and play a crucial role in predicting tumor prognosis.[7,8] In addition, some comprehensive immune-inflammation biomarkers, such as the systemic immune-inflammation index (SII), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and neutrophil to lymphocyte ratio (NLR), also have certain prognostic value for assessment.[9,10] The pan-immune-inflammation value (PIV) is a comprehensive immune inflammation biomarker that includes four parameters: neutrophils, platelets, monocytes, and lymphocytes. It more holistically reflects the balance of local immune and systemic inflammatory responses. Relevant studies have demonstrated its close association with the prognosis of various malignancies, including non-small cell lung cancer, melanoma, and prostate cancer.[11-13] Studies have also shown that the level of PIV is correlated with clinical pathological indicators such as tumor grade and tumor diameter in esophageal cancer.[14] However, there is currently a lack of research on the relationship between PIV and the clinical pathological characteristics and surgical prognosis of thyroid cancer. Therefore, this study retrospectively explored the relationship between PIV and the clinical pathological features, as well as the surgical prognosis of thyroid cancer, and investigated whether PIV has an advantage over other common inflammatory indicators.

MATERIALS AND METHODS

Study Design

Clinical data from 165 patients with thyroid cancer who underwent surgical treatment at Northern Jiangsu People's Hospital from October 2017 to October 2019 were retrospectively collected. The study was approved by the Medical Ethics Committee of Northern Jiangsu People's Hospital.

Inclusion criteria

The study included patients who had been diagnosed with thyroid cancer based on pathological examination. Eligible participants were those attending their first clinical visit, undergoing surgical treatment without any previous related therapy. Additionally, inclusion required that the patients' clinical records be complete, encompassing laboratory test results taken before treatment, detailed documentation of diagnostic and therapeutic procedures, as well as follow-up information.

Exclusion criteria

Patients were excluded from the study if they presented with severe infections or were immunosuppressed prior to surgery. Individuals who had previously undergone surgery or received any form of anti-tumor treatment were also not considered. The criteria further excluded patients with serious underlying health conditions that could interfere with tumor treatment, those with coexisting endocrine disorders, and individuals diagnosed with other types of primary malignant tumors. Furthermore, pregnant and lactating women were not eligible to participate in the study.

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Research Methods

All patients had appropriate surgical plans based on tumor stage and site of disease, intraoperative resection of pathological specimens, and timely postoperative delivery for examination.

Collection of Clinicopathological Characteristics

Patients' clinicopathological characteristics, including gender, age, body mass index (BMI), pathological type, Tumor Node Metastasis (TNM) stage, lymph node metastasis, maximum tumor diameter, and number of lesions, were collected through the hospital's medical record system.

Blood Sample Analysis

The results of routine blood tests (detected by Sysmex XN-9000 automatic hematology analyzer, Sysmex Corporation, Japan) performed within 1 week before surgery were collected, and the patients' neutrophil, monocyte, platelet, and lymphocyte counts were counted, and PIV, SII, PLR, MLR, and NLR were calculated.

PIV = (platelet count × neutrophil count × monocyte count) / lymphocyte count; SII = (platelet count × neutrophil count) / lymphocyte count; PLR=platelet count / lymphocyte count; MLR = monocyte count / lymphocyte count; NLR = neutrophil count / lymphocyte count. The best critical values of PIV, SII, PLR, MLR, and NLR were obtained by plotting the working characteristic curve (ROC) of the subjects, and the patients were categorized into high and low PIV level groups according to the best critical value of PIV.

Follow-up

After the surgery and its adjuvant treatment are completed, all patients will be followed up via telephone, outpatient clinics, or readmission. In the first three months after treatment, follow-up will be conducted every two weeks. Subsequently, follow-up will be carried out every three months within one year, and every 6 months after one year. Follow-up was performed until October 31, 2024. Disease-free survival (DFS) was observed and recorded for patients with thyroid cancer. DFS refers to the period after a patient has received surgical treatment until the tumor recurs, metastasizes, or dies of some other cause; during this period, the patient has no visible tumor presence, i.e., no signs of tumor recurrence.

Observation Indicators

(1) clinicopathological characteristics and hematological immunoinflammatory biomarker levels of the included patients; (2) prognostic predictive value of PIV versus other hematological immunoinflammatory biomarkers; (3) the relationship between different PIV levels and pathological characteristics such as age, gender, BMI, pathological type, TNM stage, lymph node metastasis, number of lesions, and maximum diameter of the tumors; (4) DFS survival analysis and its influencing factors.

Statistical Methods

Data were statistically analyzed using SPSS 23.0 statistical software and R 4.2.3 software. Measurements that conformed to normal distribution were expressed as mean ± standard deviation ($\bar{\chi} \pm s$), and those that did not conform to normal distribution were expressed as median (quartiles), i.e., M (P25, P75); counts were expressed as relative numbers or rates (n, %), and comparisons between groups were made using chi-square test/Fisher's exact test. To compare the diagnostic efficacy of PIV with other immunoinflammatory biomarkers, this study plotted ROC curves and calculated their respective area under the curve (AUC) values. In addition, the clinical applicability of PIV versus other immunoinflammatory biomarkers was assessed and compared by decision curve analysis (DCA). Survival analysis was performed using the Kaplan-Meier method, and a comparison of DFS between the 2 groups was performed using the log-rank test (log-rank test). The COX proportional risk regression analysis model was used to screen the influencing factors of DFS. Differences were considered statistically significant at $p<0.05$.

RESULTS

Characteristics of Included Patients

Among the 165 patients included in the study, females were the majority, with ages ranging from 23 to 69 years and an average age of (54.16±11.04) years; Papillary Thyroid Carcinoma was the most common pathological type. Most patients had tumors smaller than 2 cm in diameter, predominantly with single lesions. Lymph node metastasis was relatively common among the patients, and the TNM staging indicated that about half of the patients were at an earlier stage. For details, see Table 1.

Prognostic Value of Immune-Inflammatory Biomarkers

The ROC curves of PIV, SII, PLR, MLR, and NLR in the diagnosis of postoperative DFS of patients with thyroid cancer were drawn, and DCA analysis was performed. The results showed that the optimal cut-off values of PIV, SII, PLR, MLR, and NLR were 417.76, 644.32, 126.47, 0.16, and 2.09, respectively. Compared with other classical immune-inflammatory biomarkers, PIV had the largest AUC and the highest clinical utility. See Table 2, Figure 1, and Figure 2 for details.

Table 1. Clinicopathological characteristics and hematological indicators of thyroid cancer patients

Index	Sort	Data (n=165)	Index	Sort	Data (n=165)
Gender	Male	53 (32.12)	Lymph node metastasis	no	64 (38.79)
	Female	112 (67.88)		yes	101 (61.21)
Age, y	<60	98 (59.39)	Maximum tumor diameter	<2 cm	112 (67.88)
	≥60	67 (40.61)		≥2 cm	53 (32.12)
BMI, kg/m^2	<25	94 (56.97)	Number of lesions	A single lesion	102 (61.82)
	≥25	71 (43.03)		Multiple lesions	63 (38.18)
Pathological type	Papillary thyroid carcinoma	104 (63.03)	PIV	-	364.58 (237.13,522.61)
	Follicular thyroid carcinoma	36 (21.82)	SII	-	785.61 (576.31,1151.73)
	Medullary thyroid carcinoma	8 (4.85)	PLR	-	150.79 (121.09,199.06)
	Anaplastic thyroid carcinoma	17 (10.30)	MLR	-	0.24 (0.18,0.32)
TNM staging	I and II	96 (58.18)	NLR	-	2.64 (1.99,3.84)
	III and IV	69 (41.82)			

BMI: body mass index; PIV: pan-immune-inflammation value; SII: systemic immune inflammation index; PLR: platelet to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; TNM: Tumor Node Metastasis.

Table 2. The predictive value of PIV, SII, PLR, MLR, and NLR for postoperative DFS in patients with thyroid cancer

Curve	AUC	Specificity (%)	Sensitivity (%)	95% CI	Cutoff value	Youden index
PIV	0.700	70.59	60.32	0.624-0.768	417.76	0.3091
SII	0.654	44.12	80.95	0.576-0.726	644.32	0.2507
PLR	0.571	38.24	77.78	0.492-0.647	126.47	0.1601
MLR	0.581	25.49	92.06	0.502-0.658	0.16	0.1755
NLR	0.632	40.20	84.13	0.553-0.706	2.09	0.2432

PIV: pan-immune-inflammation value; SII: systemic immune inflammation index; PLR: platelet to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio.

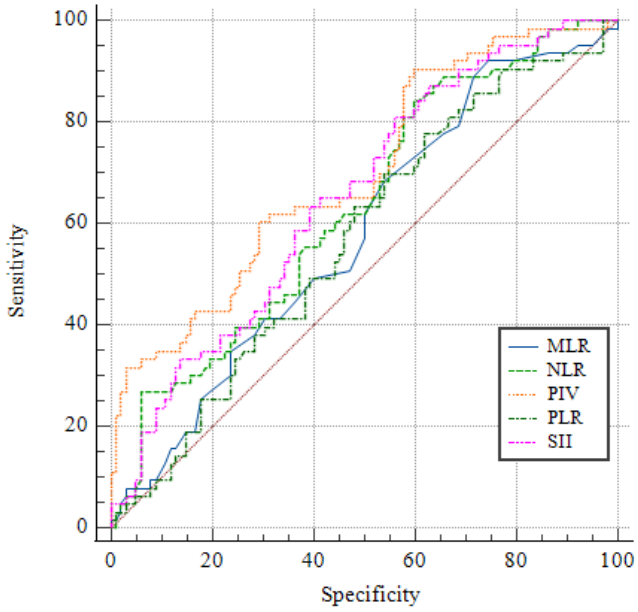

Figure 1. ROC curve analysis of PIV, SII, PLR, MLR, and NLR for predicting DFS. DCA: decision curve analysis; DFS: disease-free survival; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; PIV: pan-immune-inflammation value; PLR: platelet to lymphocyte ratio; ROC: receiver operating characteristic; SII: systemic immune inflammation index.

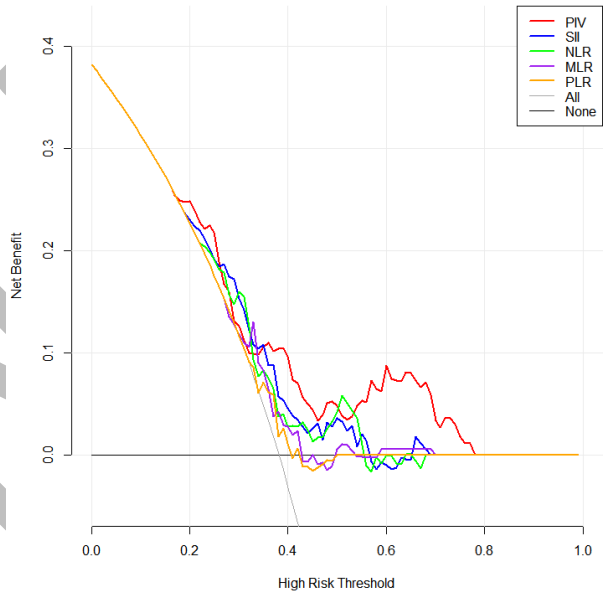

Figure 2. DCA curves of PIV, SII, PLR, MLR, and NLR for predicting DFS. DCA: decision curve analysis; DFS: disease-free survival; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; PIV: pan-immune-inflammation value; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index.

Relationship between PIV and Clinicopathologic Characteristics of Patients

Patients were divided into a high PIV level group (PIV>417.76, n=68) and a low PIV level group (PIV≤417.76, n=97) based on the optimal cutoff value of PIV before treatment, and the relationship between the different levels of PIV and the clinicopathological characteristics of thyroid cancer patients was analyzed.

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The results found that the percentage of patients whose pathological type was Papillary Thyroid Carcinoma in the PIV high-level group was significantly smaller than that in the PIV low-level group, and the percentage of patients whose pathological type was Anaplastic Thyroid Carcinoma was significantly higher than that in the PIV low-level group; moreover, the percentage of patients with stage III-IV, lymph node metastasis, maximum tumor diameter ≥2 cm, and number of foci of multiple occurrence in the PIV high-level group was higher than that in the PIV low-level group, and the difference was statistically significant ($p < 0.05$). For details, see Table 3.

Analysis OF SURVIVAL

Follow-up ended on October 31, 2024. Sixty-three patients had recurrence, metastasis, or death after surgery, and the incidence of poor prognosis was 38.18% (63/165). The DFS of 165 patients with thyroid cancer after surgery was 4-85 months, and the median DFS was 65 months. Kaplan-Meier curve analysis of DFS and log-rank test results showed that the DFS of the PIV high-level group was significantly shorter than that of the PIV low-level group (x^2=13.71, p=0.0002), as shown in Figure 3.

The Influencing Factors of DFS Were Analyzed Using Univariate COX Regression Analysis

The results of univariate Cox regression analysis showed that TNM stage, lymph node metastasis, maximum tumor diameter, and PIV level were closely associated with DFS after surgery in patients with thyroid cancer (all p<0.05). For details, see Table 4.

Table 3. Relationship between PIV and clinicopathologic features in patients with thyroid cancer

Index	Sort	Total cases (n=165)	PIV high-level group(n=68)	PIV low-level group(n=97)	x^2 value	p
Gender	Male	53 (32.12)	21 (30.88)	32 (32.99)	0.081	0.775
	Female	112 (67.88)	47 (69.12)	65 (67.01)		
Age, y	<60	98 (59.39)	43 (63.24)	55 (56.70)	0.708	0.400
	≥60	67 (40.61)	25 (36.76)	42 (43.30)		
BMI, kg/m^2	<25	94 (56.97)	37 (54.41)	57 (58.76)	0.309	0.578
	≥25	71 (43.03)	31 (45.59)	40 (41.24)		
Pathological type	Papillary thyroid carcinoma	104 (63.03)	35 (51.47)	69 (71.13)	8.358	0.039
	Follicular thyroid carcinoma	36 (21.82)	19 (27.94)	17 (17.53)		
	Medullary thyroid carcinoma	8 (4.85)	3 (4.41)	5 (5.15)		
	Anaplastic thyroid carcinoma	17 (10.30)	11 (16.18)	6 (6.19)		
TNM staging	I and II	96 (58.18)	32 (47.06)	64 (65.98)	5.882	0.015
	III and IV	69 (41.82)	36 (52.94)	33 (34.02)		
Lymph node metastasis	No	64 (38.79)	19 (27.94)	45 (46.39)	5.732	0.017
	yes	101 (61.21)	49 (72.06)	52 (53.61)		
Maximum tumor diameter	<2cm	112 (67.88)	40 (58.83)	72 (74.23)	4.350	0.037
	≥2cm	53 (32.12)	28 (41.17)	25 (25.77)		
Number of lesions	A single lesion	102 (61.82)	35 (51.47)	67 (69.07)	5.247	0.022
	Multiple lesions	63 (38.18)	33 (48.53)	30 (30.93)		

BMI: body mass index; PIV: pan-immune-inflammation value; TNM: Tumor Node Metastasis.

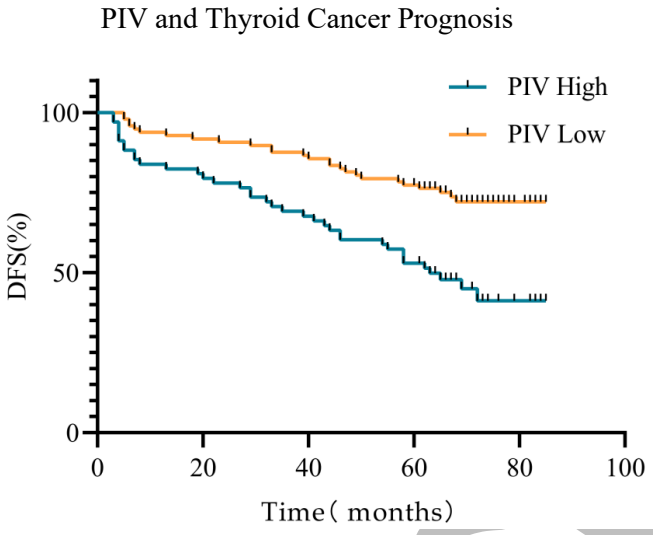

Figure 3. Comparison of disease-free survival (DFS) at high versus low pan-immune-inflammation value (PIV) levels

Table 4. One-way Cox regression analysis of postoperative DFS in thyroid cancer patients

Characteristic	N	HR	95% CI	*p*
Gender				
Male	53	Reference	-	-
Female	112	1.229	0.711–2.123	0.460
Age, y				
<60	98	Reference	-	-
≥60	67	1.337	0.815–2.192	0.250
BMI, kg/m^2				
<25	94	Reference	-	-
≥25	71	1.136	0.692–1.865	0.613
TNM staging				
I and II	96	Reference	-	-
III and IV	69	4.141	2.447–7.007	<0.001
Lymph node metastasis				
No	64	Reference	-	-
Yes	101	2.648	1.481–3.689	4.737
Maximum tumor diameter				
<2 cm	112	Reference	-	-
≥2 cm	53	3.315	2.016–5.450	<0.001
Number of lesions				
Single	102	Reference	-	-
Multiple	63	1.206	0.718–2.025	0.476
PIV				
Low level	97	Reference	-	-
High level	68	2.563	1.550–4.238	<0.001

Due to the 100% 5-year recurrence rate of anaplastic thyroid cancer among the pathological types, this may lead to the violation of certain statistical assumptions in the model, such as the proportional hazards assumption, which affects the accuracy and reliability of the model. Therefore, it is not included in the Cox regression analysis. BMI: body mass index; PIV: pan-immune-inflammation value; TNM: Tumor Node Metastasis.

Multifactor COX Regression Analysis

Based on the results of the univariate COX regression analysis in 2.5.1, the screened statistically different indicators were introduced into the multivariate COX regression analysis model, which showed that the maximum tumor diameter of ≥2 cm, TNM stage (III-IV), having lymph node metastasis, and high level of PIV were the risk factors affecting the postoperative DFS of patients with thyroid cancer (p<0.05); compared with the PIV low-level group, the risk of poor prognosis was 1.888 times higher in the PIV high-level group [hazard ratio (HR)=1.888, 95% confidence interval (CI) (1.133-3.147)]. See Table 5 for details.

Table 5. Multifactorial Cox regression analysis of postoperative DFS in patients with thyroid cancer

Variables of interest	β value	SE value	Wald value	*p*	HR value (95% CI)
Maximum tumor diameter ≥2 cm	0.693	0.275	6.325	0.012	1.999 (1.165–3.431)
TNM stage (III-IV)	0.952	0.293	10.559	0.001	2.590 (1.459–4.598)
Having lymph node metastasis	0.770	0.297	6.706	0.010	2.160 (1.206–3.868)
High level of PIV	0.636	0.261	5.949	0.015	1.888 (1.133–3.147)

PIV: pan-immune-inflammation value; TNM: Tumor Node Metastasis.

DISCUSSION

According to clinical studies and epidemiologic investigations, the development of thyroid cancer has been associated with genetic mutations, a history of exposure to radioactive materials, female hormonal abnormalities, and heredity.[15,16] These factors work together comprehensively, resulting in obvious characteristics in the population distribution of thyroid cancer. Similar to the results of other studies, this study found that thyroid cancer is more common in women (the male-to-female ratio is approximately 3:7), and it mainly occurs in individuals under the age of 60. Multiple previous studies have shown that estrogen receptors are expressed in thyroid cancer tissues. Estrogen itself may be a carcinogen, and the enhanced 2-hydroxylation reaction in its metabolism may be related to the occurrence of thyroid cancer.[17] In addition, during special periods such as pregnancy and menstruation, women experience significant hormonal fluctuations, which can disrupt the internal environment of the thyroid gland and increase the risk of developing the disease. The incidence data of thyroid cancer among white people of different genders and age groups in the United States from 1973 to 2013 show that the incidence rate is high among women of childbearing age. Before the age of 60, the incidence rate of thyroid cancer in women increases with age, and it gradually decreases after the age of 60.[18] From the perspective of age, people under the age of 60 are more likely to be exposed to ionizing radiation due to their living and working environments. Moreover, they often have bad habits such as staying up late and excessive intake of stimulating foods. These internal and external factors make thyroid cells prone to genetic mutations, significantly increasing the risk of developing thyroid cancer.[19] In addition, young people face fierce social competition and are under long-term high mental pressure, which disrupts the normal function of the body's immune system and severely weakens the immune system's ability to monitor and promptly eliminate abnormal thyroid cells, adding hidden dangers to the occurrence of thyroid cancer.[20]

Studies have shown that the immune status of patients with thyroid cancer has a significant impact on the development and outcome of the tumor.[21] In the immune function of the body, the main component that exerts an anti-tumor effect is cellular immunity, that is, the immune response mediated by specific cells (T cell subsets) and non-specific cells (macrophages, natural killer cells). Mature T cells in peripheral blood, namely $CD3^+$ T cells, can be further divided into $CD4^+$ T cells and $CD8^+$ T cells according to the different expressions of CD4 and CD8. $CD4^+$ T cells can assist B cells in

differentiating and producing antibodies, while $CD8^+$ T cells play an anti-tumor role by directly killing infected cells or tumor cells. The balance between the two is crucial for maintaining the normal immune response of the body.[22] Natural killer cells play an important role in anti-tumor immunity and curbing tumor spread. They are capable of exerting a powerful cytotoxic effect on tumor cells, thereby preventing the early spread of tumors.[23] Under normal circumstances, the number of T cells and their various subsets in the body are relatively stable, and they play an important role in the human anti-tumor immune response.[24] Studies have shown that the levels of $CD4^+$ T cells, the CD4/CD8 ratio, and the activity of natural killer cells in patients with thyroid cancer are significantly lower than those in normal individuals, while the activity of $CD8^+$ T cells is increased. Moreover, this phenomenon becomes more pronounced with the progression of the TNM staging.[25] The continuous decline of $CD4^+$ T cells and the CD4/CD8 ratio may be associated with the recurrence of thyroid cancer.[26] These results suggest that cellular immunity may play a certain role in patients with thyroid cancer; the combined application of immunological biomarkers is expected to become an effective indicator for the early detection of papillary thyroid carcinoma. However, the detection of cellular immune indices like $CD4^+$ T cells and $CD8^+$ T cells requires professional equipment and personnel, and the high cost restricts their large-scale clinical application. With the in-depth understanding of the role mechanism of inflammation in the occurrence and development of malignant tumors, peripheral blood inflammatory indices have been found to be associated with the prognosis of tumors. Currently, there is an urgent need for simple, economical, and reliable indices to evaluate the immune and inflammatory status of patients with thyroid cancer. The calculation of the PIV index is simple. It only needs a routine blood test and doesn't require complex equipment or techniques. Moreover, in various malignant tumors, the PIV index is related to tumor staging, metastasis, and prognosis.

The results of this study revealed that patients with thyroid cancer with large tumor diameter, TNM stage III-IV, lymph node metastasis, multiple foci, and the pathological type of Anaplastic Thyroid Carcinoma had higher baseline values of PIV. This indicates that the PIV level is related to the pathological type of thyroid cancer, TNM staging, the number of lesions, tumor size, and the presence of lymph node metastasis. It suggests that an increase in the PIV level may be involved in the progression of thyroid cancer. PIV is composed of neutrophils, platelets, monocytes, and lymphocytes. The routine blood tests of patients with high PIV often show an "inflammatory blood picture" (neutrophils increased, lymphocytes decreased). Lymphocytes are the core cells of the immune system, including T lymphocytes, B lymphocytes, and natural killer cells. They can eliminate pathogens, tumor cells, etc., through cellular immunity and humoral immunity mechanisms. At the same time, they release inflammatory mediators such as cytokines and participate in the regulation of the inflammatory response, thereby inhibiting the proliferation and migration of tumor cells.[27] When the number of lymphocytes in the blood circulation is relatively reduced, it may imply a decrease in the number of lymphocytes in the tissue adjacent to the cancer, which weakens the anti-tumor immune response mediated by them. As a result, a tumor microenvironment that is conducive to the proliferation and metastasis of cancer cells is formed. Monocytes are also major immune cells in the body. Inflammation can trigger the movement of monocytes from the bone marrow to the peripheral blood, and they differentiate into tumor-associated macrophages (TAMs) and dendritic cells.[28,29] Therefore, the number of circulating monocytes in the blood can indirectly reflect the number of TAMs. TAMs promote angiogenesis in tumor tissues, remodeling of the extracellular matrix of tumor cells, as well as the invasion and metastasis of tumor cells by secreting epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), interleukin-6, interleukin-10, matrix metalloproteinases, and so on.[30] In addition, some studies have pointed out that TAMs have certain immunosuppressive effects. They can upregulate the expression of programmed death-1 (PD-1), thus creating a microenvironment of local immunosuppression that facilitates the immune escape of tumor cells.[31] Neutrophils can inhibit tumor necrosis factor (TNF)-α and promote the release of VEGF. The overexpression of VEGF can induce the formation of new blood vessels in tumors, thereby facilitating tumor growth and metastasis.[32,33] Studies have shown that patients with advanced tumors often have thrombocytosis,[34] and platelets can increase angiogenesis by releasing mediators such as VEGF and TNF-β to promote tumor growth and survival.[35] Therefore, the platelet to immune cell ratio calculated from neutrophils, platelets, monocytes, and lymphocytes can reflect the status of

infiltrating immune cells in thyroid cancer, and is associated with the progression of thyroid cancer.

Notably, compared with other well-established and commonly used immunoinflammatory biomarkers, including SII, PLR, MLR, and NLR, PIV demonstrated superior efficacy and clinical applicability in ROC and DCA curves for evaluating the surgical prognosis of thyroid cancer patients. SII, PLR, MLR, and NLR are composed of 2 to 3 types of cells, including neutrophils, lymphocytes, platelets, and monocytes. In contrast, PIV incorporates all four of these inflammatory and immune response indicators, providing a more comprehensive reflection of the body's systemic inflammation and immune status. The predictive value of PIV was confirmed in a meta-analysis covering 15 studies of various types of cancer.[36] In addition, the prognostic role of PIV in a variety of malignancies receiving immunotherapy has also been demonstrated.[37,38]

In a study of operable breast cancer patients, it was observed that PIV was an independent influencer of overall survival (OS) in operable breast cancer patients.[39] In the present study, we also came up with similar results that PIV was an independent influence on postoperative DFS in patients with thyroid cancer, and patients with high levels of PIV had a 1.888-fold increased risk of poor prognosis compared to patients with low levels of PIV [HR=1.888, 95% CI(1.133-3.147)]. Meanwhile, this study further compared the DFS survival curves of patients with different levels of PIV thyroid and showed that the DFS of patients with high PIV was significantly shorter than that of patients with low PIV. This further suggests that PIV is a good predictor of postoperative tumor-free survival in thyroid cancer patients. The overall level of immunity in thyroid cancer is high, which allows multiple immune cells to exert pro- or anti-tumor effects through different pathways, creating a favorable immune landscape.[40,41] When PIV levels are elevated, the balance between the patient's anti-tumor inflammatory response and immune function is disrupted, driving the disease in a direction that promotes tumorigenesis and metastasis, ultimately leading to a poor patient prognosis. It also suggests that symptomatic interventions such as anti-inflammatory and immunity-enhancing treatments can be given to patients according to their PIV levels before surgical treatment to improve their prognosis.

Limitations of this study: (1) it was a single-center retrospective study with some selection bias; (2) it only evaluated PIV on admission and failed to analyze the data of PIV after surgery, which combined with the postoperative changes in PIV may allow for a more accurate assessment of the prognosis; (3) there was a lack of information on the postoperative adjuvant treatment of the patients, and therefore, the differences in the postoperative adjuvant treatment of the patients were not elucidated in the article；(4) since this study is a retrospective one, it was unable to simultaneously detect the specific immune biomarkers in the tumor microenvironment to analyze the direct relationship between PIV and the local immune response. In the future, multicenter prospective studies can be carried out. It is necessary to comprehensively collect information on postoperative adjuvant therapy, simultaneously detect the specific immune biomarkers in the tumor microenvironment, and dynamically monitor the changes of PIV after surgery, to more accurately evaluate the prognosis and analyze its mechanism of action.

In summary, there is a close association between PIV values and TNM stage, lymph node metastasis, maximum tumor diameter, and number of lesions in thyroid cancer patients, while high levels of PIV are independent risk factors for DFS and can be used as an important predictor of surgical prognosis.

STATEMENT OF ETHICS

This experiment was approved by the Northern Jiangsu People's Hospital Ethics Committee (No. 2022ky204).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The original contributions presented in the study are included in the article. Further inquiries can be directed

to the corresponding authors (email: vicoastthrough@hotmail.com).

AI ASSISTANCE DISCLOSURE

Not applicable.

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