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Original Article

Predictive value of systemic inflammatory response index for the occurrence and prognosis of lung metastases in papillary thyroid carcinoma

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Abstract: Objective: To investigate the predictive value of the systemic immune-inflammation index (SIRI) for the timing and prognosis of lung metastases in patients with papillary thyroid carcinoma (PTC) post-surgery and before the first ^{131}I ablation therapy. Methods: This retrospective study collected clinical data from 234 outpatients who underwent total or subtotal thyroidectomy followed by their first ^{131}I ablation therapy. Patients were divided into two groups: a lung metastasis group (n=78) and a PTC control group (n=156). The optimal cutoff value for SIRI in the development of lung metastases was determined using receiver operating characteristic (ROC) curves. The 78 patients with lung metastases were further divided into a high SIRI group (n=60) and a low SIRI group (n=18). Results: Statistically significant differences were found between the groups in terms of SIRI, pre-ablation thyroglobulin (Ps-Tg), maximum tumor diameter, and whether the tumor was multifocal (all P<0.05). Patients with higher SIRI values, higher Ps-Tg levels, larger main tumors, and more multiple tumors were more likely to develop lung metastases (all P<0.05). SIRI was effective in diagnosing lung metastases in patients with PTC, with an area under the curve (AUC) of 0.834 and an optimal cutoff value of 0.64. Overall, in all cases, the disease control rate and progression-free survival were significantly higher in the low-SIRI group than in the high-SIRI group (both P<0.05). Conclusion: SIRI prior to the first ^{131}I treatment has good predictive value for the occurrence of postoperative lung metastases and prognosis in PTC patients.

Keywords: Systemic inflammatory response index, papillary thyroid carcinoma, lung metastasis, radioiodine therapy, treatment effect

Introduction

Thyroid cancer is a cancerous tumor that develops from the epithelial cells and parafollicular cells of the follicles in the thyroid region [1, 2]. According to data from the International Agency for Research on Cancer (IARC), a branch of the World Health Organization, thyroid cancer ranks 7th in incidence among all cancers worldwide; and 5th in incidence among cancers in women (IARC, 2020). There are three main types of thyroid cancer: differentiated thyroid cancer, medullary thyroid cancer, and undifferentiated thyroid cancer. Among them, differentiated thyroid cancer (DTC) includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), and PTC is currently the most common type of all thyroid cancers [4]. The overall prognosis of PTC is relatively good, with a high survival rate following standard treatment (surgery, radioactive iodine therapy). However, some patients develop more aggressive PTC. The most significant predictor of poor prognosis in PTC is distant metastasis, which increases disease-specific mortality. Among the many sites of metastasis, the lungs are the most common. Lung metastases present in diverse forms, ranging from small micronodules sensitive to radioactive iodine therapy, to large, more difficult-to-treat metastases that are insensitive to iodine. This underscores the critical importance of timely identification and assessment of the risks faced by patients at risk of developing these conditions [7, 8].

Cancer progression and spread is a complex process in which the intrinsic characteristics

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of tumor cells, the host's systemic environment, and the local microenvironment all play crucial roles. Chronic inflammation is a hallmark of cancer, driving its development, progression, and metastasis. Systemic inflammatory responses in peripheral blood cells can serve as a convenient window for observing host-tumor interactions [9, 10].

Systemic immune-inflammation index (SIRI) is an emerging inflammatory marker calculated from neutrophils, monocytes, and lymphocytes. Numerous studies have shown that SIRI has predictive value for survival in various diseases, such as pancreatic cancer [11] and rectal cancer [12]. In the case of thyroid cancer, inflammatory markers like SIRI have been found to predict lymph node metastasis in patients with papillary thyroid carcinoma [13].

However, there is currently a significant gap in understanding in this area. The SIRI has received limited attention as a predictor of distant metastasis, with a particular focus on the lungs as the most critical site of metastasis. Furthermore, it remains unclear whether measuring SIRI before additional treatment helps identify which patients have a worse prognosis after developing lung metastases, or which patients may respond poorly to conventional radioactive iodine therapy.

Therefore, to fill these gaps, this study hypothesizes that in patients with PTC and lung metastases, higher SIRI (including values post-surgery and before the first radioactive iodine ablation therapy) may be more likely to lead to lung metastasis, poor recovery, and an increased risk of death. The primary objective of this study is to determine whether SIRI can predict the occurrence of lung metastases and the prognosis of patients with lung metastases. We will conduct a retrospective study of patients with PTC to explore these questions.

Materials and methods

Study population and eligibility

This retrospective cohort study was conducted in the Department of Nuclear Medicine, Affiliated Hospital of Xuzhou Medical University. The study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Approval No.: XYFY2023-KL485-01). Due to the retrospective nature of this study, we analyzed anonymized clinical databases, thus exempting informed consent. All procedures were performed in accordance with the ethical standards of the Institutional Research Committee and the Declaration of Helsinki 1964 and its subsequent revisions.

This study initially included 78 PTC patients who underwent total or partial thyroidectomy, subsequently developed lung metastases, and received ^{131}I therapy in the Department of Nuclear Medicine, Affiliated Hospital of Xuzhou Medical University between September 2018 and December 2023. The mean age of the patients was 44.19 ± 17.19 years. The inclusion criteria for lung metastasis were: (1) Patients who underwent total or subtotal thyroidectomy at the Affiliated Hospital of Xuzhou Medical University and were diagnosed with PTC postoperatively; (2) Patients who received ^{131}I treatment in the Department of Nuclear Medicine of the hospital and had complete imaging and serological data; (3) Patients whose ^{131}I whole-body scintigraphy (^{131}I-WBS) indicated lung metastasis of thyroid cancer, confirmed by CT and single-photon emission computed tomography (SPECT), with the largest metastatic lesion diameter ≥10 mm; and (4) Patients with only distant lung metastasis, regardless of whether there was cervical lymph node metastasis. In addition, 156 patients who underwent total or subtotal thyroidectomy and ^{131}I treatment at the same institution and had no distant metastasis, lung inflammation or other tumors were selected as the control group, with a mean age of 44.66 ± 13.26 years. The most important exclusion criteria for both groups were: (1) Incomplete clinical data; (2) Presence of inflammation or autoimmune disease; (3) ^{131}I-WBS showing no abnormal pulmonary uptake, including patients with lung metastases but no iodine uptake; (4) Other distant metastases, such as bone or brain metastases; and (5) Positive thyroglobulin antibody (anti-thyroglobulin antibody, TgAb) (TgAb>115 IU/ml) (**Figure 1**).

Clinical and laboratory data collection

Demographic and clinicopathological data, including age, sex, type of thyroidectomy (total or subtotal), and detailed histopathological features from the surgical specimen report,

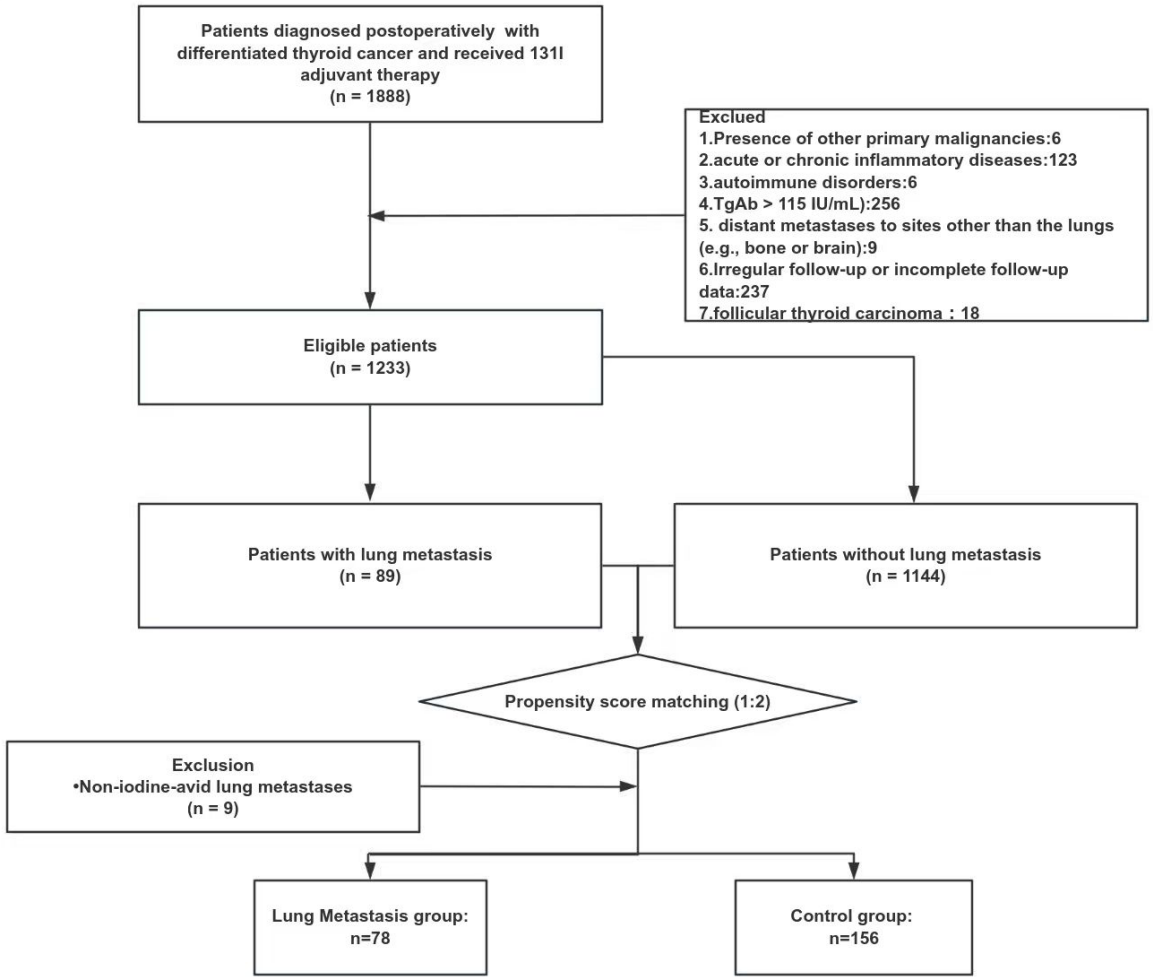

Figure 1. Flowchart of participant enrollment.

were extracted from electronic medical records. Pathological tumor (pT) staging and lymph node (pN) status were determined according to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition [14]. Specific features recorded included: maximum tumor diameter (in centimeters), focal tumor (single or multifocal), presence of capsule invasion, and evidence of neurological invasion. Peripheral venous blood was collected from all participants one day prior to their first ^{131}I treatment, after a 12-hour fast. Complete blood counts (CBCs) were performed immediately, including red blood cell count, hemoglobin count, platelet count, absolute neutrophil count, absolute lymphocyte count, and absolute monocyte count, and these tests were performed on every sample. These hematological parameters were obtained using clinical-grade automated hematology analyzers: Sysmex XN-550 (Kobe, Japan) and Beckman Coulter DxH 900 (Breakman Coulter, USA). The SIRI was calculated for each patient using the following formula: SIRI = Absolute Neutrophil Count × Absolute Monocyte Count ÷ Absolute Lymphocyte Count. Pre-treatment thyroid-related data and CBC results were extracted from clinical records. Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were measured using the cobas e801 chemiluminescent immunoassay from Roche Diagnostics, Switzerland.

^{131}I treatment process and protocol

Following total or subtotal thyroidectomy, all patients should discontinue levothyroxine for 3-4 weeks and avoid iodine-containing foods for 1-2 weeks to ensure adequate thyroid-stimulating hormone (TSH) levels in the blood,

exceeding 30 mIU/L. According to the 2025 American Thyroid Association (ATA) guidelines, the dose for patients receiving ^{131}I therapy for the first time without any evidence of distant metastasis is 2.96-5.55 GBq (80-150 mCi). For patients with lung metastases from thyroid cancer, the dose should be 3.7-7.4 GBq (100-200 mCi). For patients over 70 years of age, the dose is 3.7-5.5 GBq (100-150 mCi).

Treatment response assessment in patients with lung metastases

Patients with lung metastases following PTC surgery or ^{131}I therapy should be followed up every 3 to 12 months. According to the 2025 American Thyroid Association (ATA) guidelines [2], if a patient has biopsy-confirmed local/regional or distant metastases, or structural iodine resistance (SIR), lung metastases should be identified by pathological examination or CT, SPECT, or ^{131}I-WBS and the efficacy should be evaluated according to the Recognition of Efficacy in Solid Tumors version 1.1 (RECIST 1.1). If there are two or more measurable metastatic lymph nodes in the lungs, and each lymph node is not less than 10 mm in size, two should be selected as target lesions; the largest lung metastasis refers to the largest diameter of a single target lesion or the maximum of the sum of the diameters of the two longest target lesions. Based on the change in the maximum diameter of the target lesion or the sum of the maximum diameters of the target lesions, it is determined to belong to one of the following categories: (1) Complete remission (CR): All target lesions completely disappeared; (2) Partial remission (PR): The sum of the target lesion sizes decreased by more than 30% compared to the original size; (3) Stable disease (SD): The criteria for partial remission or disease progression were not met; (4) Disease progression (PD): The sum of the target lesion sizes increased by more than 20% or increased by 5 mm, and new lesions appeared. Disease control rate (DCR) = (CR + PR + SD)/Number of evaluable patients × 100%.

Statistical methods

Statistical analysis was performed using SPSS version 27.0. Propensity score matching (PSM) was used to balance covariates between the control group and the lung metastasis group. Categorical data were expressed as cases (%), and chi-square test was used for comparisons between groups; normally distributed quantitative and continuous data were expressed as mean ± standard deviation, and independent samples t-test was used. Conversely, for non-normally distributed continuous variables, the median (interquartile range) was used, and the Mann-Whitney U test was employed for analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value for the SIRI for predicting lung metastasis using the Youden index. The Kaplan-Meier method was used to plot survival curves. Multivariate logistic regression analysis was performed on risk factors for lung metastasis in PTC patients. For patients with lung metastasis, independent predictors of progression-free survival (PFS) were identified using univariate and multivariate Cox proportional hazards models. Variables with a p-value <0.05 in the univariate analysis were included in the multivariate model. A p-value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

There were no differences between the PTC control group and the lung metastasis group in terms of gender, age, surgical method, cervical lymph node metastasis, and capsule invasion (all P>0.05). However, there were differences between the two groups in pre-ablation thyroglobulin (Ps-Tg), maximum tumor size, T stage, whether the tumor was solitary, and nerve invasion (all P<0.05, **Table 1**).

Preoperative thyroid function and some basic hematological parameters were comparable between the control group and the lung metastasis group, with no statistically significant differences (all P>0.05, **Table 2**). However, there was a significant difference between the two groups in terms of SIRI (P<0.05).

Independent influencing factors of lung metastasis

This study used six indicators (SIRI, Ps-Tg, maximum tumor diameter, T stage, whether the tumor was solitary, and whether nerve invasion was present) with P values <0.05 in univariate analysis as independent variables to establish

Table 1. Comparison of clinical and pathological features between the PTC control group and the pulmonary metastasis group (n%) or (P25, P75)

Indicator	Case (n=234)	Control (n=156)	Metastasis (n=78)	Statistic	P
Age (Years)	44.50 ± 14.65	44.66 ± 13.26	44.19 ± 17.19	t=0.21	0.833
SIRI (×10^9/L)	0.58 (0.46, 0.75)	0.52 (0.42, 0.64)	0.85 (0.65, 1.15)	Z=-8.32	<.001
Ps-Tg (IU/mL)	8.29 (1.96, 31.16)	4.57 (0.80, 14.88)	39.89 (9.11, 316.68)	Z=-7.59	<.001
Maximum tumor diameter (cm)	1.50 (0.83, 2.18)	1.00 (0.80, 1.80)	2.00 (1.40, 3.00)	Z=-5.45	<.001
Gender, n (%)				χ^2=3.20	0.073
Female	173 (73.93)	121 (77.56)	52 (66.67)		
Male	61 (26.07)	35 (22.44)	26 (33.33)		
T staging/case (%)				χ^2=13.00	<.001
T1/T2	117 (50.00)	91 (58.33)	26 (33.33)		
T3/T4	117 (50.00)	65 (41.67)	52 (66.67)		
N staging/case (%)				χ^2=1.91	0.384
N0	14 (5.98)	11 (7.05)	3 (3.85)		
N1a	98 (41.88)	68 (43.59)	30 (38.46)		
N1b	122 (52.14)	77 (49.36)	45 (57.69)		
Surgical type/case (%)				χ^2=0.91	0.341
Total	174 (74.36)	113 (72.44)	61 (78.21)		
Subtotal	60 (25.64)	43 (27.56)	17 (21.79)		
Solitary/case (%)				χ^2=18.61	<.001
Yes	66 (28.21)	58 (37.18)	8 (10.26)		
No	168 (71.79)	98 (62.82)	70 (89.74)		
Membrane invasion/case (%)				χ^2=1.82	0.178
No	64 (27.35)	47 (30.13)	17 (21.79)		
Yes	170 (72.65)	109 (69.87)	61 (78.21)		
Nerve invasion/case (%)				χ^2=21.08	<.001
No	200 (85.47)	145 (92.95)	55 (70.51)		
Yes	34 (14.53)	11 (7.05)	23 (29.49)		

SIRI: Systemic Inflammation Response Index; Ps-Tg: Preablative Stimulated Thyroglobulin.

Table 2. Comparison of preoperative thyroid function and complete blood count parameters between groups (means ± standard) or (P25, P75)

Indicator	Case (n=234)	Control (n=156)	Metastasis (n=78)	Statistic	P
TSH (mIU/L)	2.13 ± 1.86	2.15 ± 1.79	2.08 ± 1.98	t=0.55	0.580
FT3 (pmol/L)	4.78 ± 0.73	4.80 ± 0.72	4.73 ± 0.76	t=0.71	0.480
FT4 (pmol/L)	16.08 ± 2.19	16.19 ± 2.14	15.87 ± 2.29	t=1.04	0.300
RBC (×10^{12}/L)	4.28 ± 0.53	4.31 ± 0.51	4.21 ± 0.57	t=1.34	0.181
Hb (g/L)	131.65 ± 15.02	132.52 ± 14.22	129.82 ± 16.45	t=1.30	0.196
PLT (×10^9/L)	220.45 ± 48.33	218.67 ± 46.58	224.12 ± 51.78	t=0.81	0.417
SIRI (×10^9/L)	0.58 (0.46, 0.75)	0.52 (0.42, 0.64)	0.85 (0.65, 1.15)	Z=-8.32	<.001

SH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; RBC: Red blood cell count; Hb: Hemoglobin; PLT: Platelet count.

a logistic regression model. The results showed that SIRI, Ps-Tg, maximum tumor diameter, and whether the tumor was solitary were independent factors influencing lung metastasis in PTC patients. Specifically, higher SIRI and Ps-Tg levels, and larger maximum tumor diameters,

Table 3. Multivariate logistic regression analysis of pulmonary metastasis in papillary thyroid carcinoma

Indicator	β	SE	Wald	P	OR (95% CI)
SIRI (×10^9/L)	0.598	0.101	35.41	<.001	1.819 (1.494-2.216)
Ps-Tg (IU/mL)	0.008	0.002	16.906	<.001	1.008 (1.004-1.012)
Maximum tumor diameter (cm)	0.319	0.162	3.897	0.048	1.376 (1.002-1.889)
T staging (T1/2, T3/4)	-0.698	0.483	2.089	0.148	0.497 (0.193-1.282)
Solitary	2.166	0.607	12.731	<.001	8.720 (2.655-28.641)
Nerve invasion	1.050	0.632	2.760	0.096	2.857 (0.828-9.852)

SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval; SIRI: Systemic Inflammation Response Index; Ps-Tg: Preablative Stimulated Thyroglobulin.

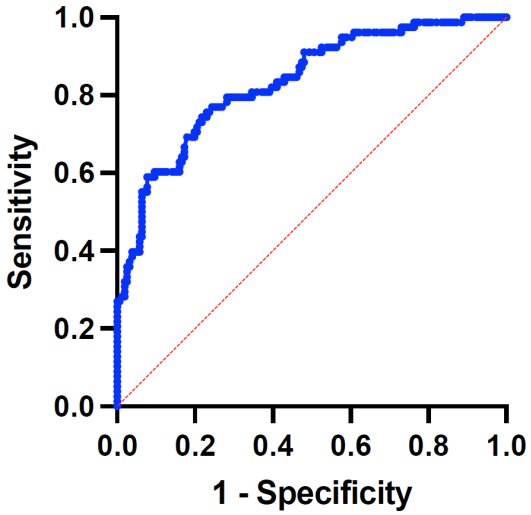

Figure 2. Predictive value of SIRI for pulmonary metastasis in PTC patients. SIRI: Systemic Inflammation Response Index; PTC: papillary thyroid carcinoma.

significantly increased the likelihood of lung metastasis in patients with multiple tumors (**Table 3**).

SIRI criterion and stratification

The optimal SIRI threshold before ^{131}I treatment in PTC patients was determined using ROC curves, and the predictive value of SIRI for PTC lung metastasis was evaluated. The AUC for SIRI in predicting lung metastasis in PTC patients was 0.834 (95% CI: 0.779-0.889), with an optimal threshold of 0.64 and a sensitivity of 76.9% (**Figure 2**). Based on this optimal threshold, 78 PTC patients with lung metastasis were further divided into a high SIRI group (SIRI>0.64, n=60) and a low SIRI group (SIRI≤0.64, n=18).

Treatment response and survival outcomes

The DCR in the low-SIRI group was significantly higher than that in the high-SIRI group (88.9% vs. 55.0%), with a statistically significant difference (P<0.01) (**Table 4**). According to the RECIST 1.1 criteria for evaluating treatment efficacy in solid tumors, the follow-up deadline for this study was June 15, 2025, with a median follow-up time of 47.3 months. Survival analysis showed that the PFS in the low-SIRI group was longer than that in the high-SIRI group: 66.9 months (95% CI: 59.4-74.3) vs. 38.8 months (95% CI: 30.9-46.7), with a statistically significant difference (P< 0.01, **Figure 3**).

Prognostic factors in patients with lung metastases

Univariate analysis of factors potentially affecting treatment outcomes in patients with lung metastases revealed that high SIRI (>0.64×10^9/L), maximum lung metastasis size ≥2 cm, and maximum tumor diameter ≥2 cm were associated with poor prognosis in patients with lung metastases (**Table 5**).

Multivariate analysis using a Cox regression model was performed on the indicators with P<0.05 in the univariate analysis. The results showed that high SIRI (>0.64×10^9/L) and maximum lung metastasis size >2 cm were independent factors leading to shortened PFS in PTC patients with pulmonary metastasis (P<0.05, **Table 6**).

Discussion

Chronic inflammation may affect the occurrence, development and spread of various cells

Table 4. Analysis of ^{131}I treatment efficacy in low and high SIRI groups

Groups	n	CR	PR	SD	PD	DCR
Low	18	0	9	7	2	16 (88.9)
High	60	1	8	24	27	33 (55.0)
p						0.003

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; DCR: Disease Control Rate; SIRI: Systemic Inflammation Response Index.

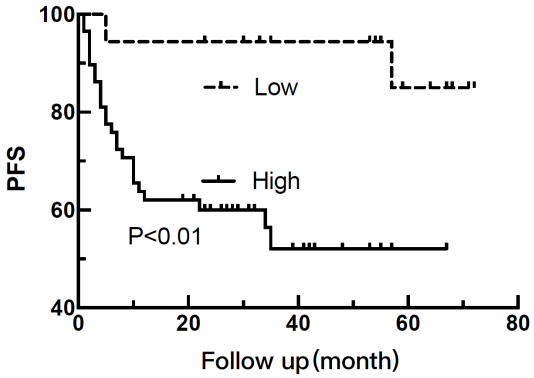

Figure 3. Comparison of Kaplan-Meier curves for PFS in different SIRI groups. PFS: progression-free survival; SIRI: Systemic Inflammation Response Index.

in the tumor microenvironment, such as neutrophils, monocytes and lymphocytes [15]. Long-term inflammatory stimulation can also lead to tumor cell proliferation and increase DNA damage and gene mutation caused by reactive oxygen species, thereby inducing cancer [16]. Neutrophils play a dual role in tumor cells. Some neutrophils help reduce tumors by acting on or destroying tumor cells; others are tumor-associated neutrophils (TANs), which support the inflammatory process of tumors through angiogenesis, body alteration, spread on tumors and deactivation of the immune system [17]. Monocytes are a type of white blood cell with many different types. They act as a bridge between the non-immune state and the immune system learning how to respond, and alter the tumor environment in a variety of ways, making it difficult for the immune system to attack tumor cells and making cancer cells easier to spread. At the same time, monocytes can activate antigen-presenting cells and can also transform into tumor-associated macrophages like dendritic cells [18]. Lymphocytes exert their anti-tumor proliferation and migration effects by inhibiting the proliferation and migration of tumor cells [17].

SIRI is a novel inflammatory marker calculated by detecting the levels of neutrophils, lymphocytes, and monocytes in peripheral blood. An elevated SIRI typically indicates an increase in neutrophils and monocytes, while lymphocytes decrease. In cancer biology, this is thought to be due to a pro-cancer and anti-immune environment in the body, which prevents the immune system from recognizing cancer and creates favorable conditions for the spread of cancer cells, thereby promoting cancer growth and metastasis [19-21]. Traditional inflammatory markers usually involve only one inflammatory cell pair, such as the neutrophil-lymphocyte ratio (NLR) and the monocyte-lymphocyte ratio. Many meta-analyses have shown that a high SIRI is associated with poor prognosis in breast cancer, colorectal cancer, and pancreatic cancer [22-24]. Wu et al. [25] found that in 1,763 patients with gastric cancer, the SIRI ranged from 0.58 to 1.35; the overall survival and disease-free survival were worse in the high SIRI group than in the low SIRI group. In differentiated thyroid cancer, Pang et al. [13] found that in 1,394 patients with cN0 stage PTC, a high SIRI was an independent positive predictor of central lymph node metastasis when the SIRI cutoff value was 0.77. Thyroid cancer is generally classified as a low-invasive tumor with a good prognosis; however, the prognosis may be poor when distant metastasis (such as lung metastasis) occurs [26]. Thyroid disease is associated with several factors that include age, clinical stage, whether the primary tumor is multifocal, and Ps-TG. Tg is a specific protein produced by the thyroid gland. Ps-TG refers to the serum Tg level when the TSH level is higher than 30 mIU/L. Ps:Tg is often used after surgery to predict whether the disease will persist or recur, to assess the treatment effect, and also for periodic risk stratification [27].

In this study, after performing multivariate logistic regression analysis on factors influencing lung metastasis, we found that the SIRI, Ps-Tg, maximum tumor diameter, and multiple tumor features were independent risk factors for lung metastasis. There may be some biological reasons behind this association, perhaps because elevated SIRI indicates a systemic condition that promotes cancer growth.

Table 5. Univariate cox analysis of prognostic factors in PTC patients with pulmonary metastasis

Indicator	β	SE	Wald	P	HR (95% CI)
Age (<55 years/≥55 years)	0.692	0.375	3.409	0.065	1.999 (0.958-4.168)
Gender (M/F)	0.228	0.384	0.351	0.553	1.256 (0.592-2.665)
SIRI (SIRI≤0.64/>0.64×10^9/L)	1.929	0.762	6.411	0.011	6.882 (1.546-30.635)
maximum pulmonary metastatic lesion size (≤2 cm/>2 cm)	1.606	0.411	15.269	<.001	4.981 (2.226-11.145)
Surgical type (Total/Subtotal)	-0.153	0.459	0.111	0.739	0.858 (0.349-2.110)
Solitary (Yes/No)	-0.650	0.612	1.127	0.288	0.522 (0.157-1.733)
maximum tumor diameter (≤2 cm/>2 cm)	0.827	0.378	4.777	0.029	2.287 (1.089-4.800)
Membrane invasion (No/Yes)	0.272	0.391	0.486	0.486	1.313 (0.611-2.824)
Nerve invasion (No/Yes)	0.294	0.391	0.562	0.453	1.341 (0.623-2.889)

SE: Standard Error; HR: Hazard Ratio; CI: Confidence Interval; SIRI: Systemic Inflammation Response Index; M: Male; F: Female.

Table 6. Multivariate cox analysis of prognostic factors in PTC patients with pulmonary metastasis

Indicator	β	SE	Wald	P	HR (95% CI)
SIRI (SIRI≤0.64/>0.64×10^9/L)	1.856	0.792	5.488	0.019	6.395 (1.354-30.205)
maximum pulmonary metastatic lesion size (≤2 cm/>2 cm)	1.458	0.433	11.319	<.001	4.299 (1.838-10.055)
maximum tumor diameter (≤2 cm/>2 cm)	0.541	0.396	1.682	0.195	1.672 (0.769-3.653)

SE: Standard Error; HR: Hazard Ratio; CI: Confidence Interval; SIRI: Systemic Inflammation Response Index.

Elevated SIRI indicates neutrophilia, monocyte proliferation, and lymphopenia, suggesting an immunosuppressive state, as this leads to the production of large amounts of pro-inflammatory cell signaling substances and growth-promoting substances. This environment is highly conducive to key metastatic processes such as epithelial-mesenchymal transition, angiogenesis, and circulating tumor cells evading the immune system. Importantly, elevated SIRI may reflect a pro-inflammatory tumor microenvironment that may downregulate the expression of sodium-iodine transporters, promoting iodine resistance and resulting in poor response to radioactive iodine therapy and a poor prognosis. Therefore, the claim that cancer cells can successfully colonize new sites such as the lungs seems plausible [28, 29]. However, according to Guideline 4, residual thyroid tissue after surgery, the final TSH level in the blood, and TgAb may interfere with this. In this study, approximately 20 of the 78 patients with lung metastases had ps-Tg levels exceeding the maximum measurable value of 500 μL on the device; however, due to the lack of protein dilution, specific data were unavailable. Therefore, I will primarily investigate the predictive value of SIRI for lung metastasis and prognosis. In our study, we found a link between high SIRI and poor treatment outcomes due to the association between systemic inflammation and tumor biology. Chronic inflammation may cause developmental reversal in thyroid cancer cells, reduce NIS production, and decrease radioactive iodine uptake. Furthermore, the inflammatory tumor environment can promote tumor survival signaling pathways and drug resistance. This explains the lower DCR and PFS in patients with high SIRI [30, 31]. In the survival analysis of the lung metastasis group, we observed that patients with low SIRI had higher PFS and DCRs than those with high SIRI. Cox regression analysis showed that SIRI>0.64×10^9/L and the largest metastatic lesion in the lung metastases being greater than 2 cm were independent predictors of lung metastasis recurrence. The presence of cervical lymph node metastasis in PTC is a major focus of most domestic and international studies on the correlation between inflammatory markers and PTC. Inflammation is associated with inflammatory indicators such as SIRI and the NLR. Gu et al. [32] found that patients with higher levels of inflammatory factors such as SIRI and NLR had a higher chance of developing cervical lymph node metastasis; however, studies on SIRI and lung metastasis in patients with PTC are relatively few.

Clinically, elevated SIRI should alert physicians to a higher risk of lung metastasis and a poorer prognosis, prompting closer follow-up and consideration of more aggressive treatment strategies. For example, patients with high SIRI may

benefit from higher initial doses of radioactive iodine therapy, or, if iodine-resistant disease develops, targeted therapy can be combined as early as possible. In this paper, we conclude that SIRI is also an independent predictor of prognosis in patients with lung metastases from PTC. However, since this study was only a single-center retrospective study with a small sample size, and we must consider the SIRI threshold of 0.58-1.35 proposed by Wu et al. [25] in their study of gastric cancer. However, our threshold is 0.64, which is slightly below this range, so there may be large individual differences in inflammatory markers. The optimal threshold is related to the number of patients involved in the study and the type of disease. The SIRI measured in this study was obtained before the first ^{131}I treatment, which may reflect postoperative inflammation rather than purely tumor-related systemic inflammation. Future studies should measure SIRI at multiple time points (preoperative, postoperative acute phase, and postoperative inflammation resolution) to better distinguish its source and optimize its predictive value. Therefore, in order to carry out future studies, multicenter data need to be collected and new biomarkers need to be found to predict the prognosis of lung metastases from PTC.

Disclosure of conflict of interest

None.

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References

[1] Forma A, Kłodnicka K, Pająk W, Flieger J, Teresińska B, Januszewski J and Baj J. Thyroid cancer: epidemiology, classification, risk factors, diagnostic and prognostic markers, and current treatment strategies. Int J Mol Sci 2025; 26: 5173.

[2] Boucai L, Zafereo M and Cabanillas ME. Thyroid cancer: a review. JAMA 2024; 331: 425-435.

[3] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[4] Ringel MD, Sosa JA, Baloch Z, Bischoff L, Bloom G, Brent GA, Brock PL, Chou R, Flavell RR, Goldner W, Grubbs EG, Haymart M, Larson SM, Leung AM, Osborne JR, Ridge JA, Robinson B, Steward DL, Tufano RP and Wirth LJ. 2025 American thyroid association management guidelines for adult patients with differentiated thyroid cancer. Thyroid 2025; 35: 841-985.

[5] Tian T, Huang S, Dai H, Qi M, Liu B and Huang R. Radioactive iodine-refractory pulmonary metastases of papillary thyroid cancer in children, adolescents, and young adults. J Clin Endocrinol Metab 2023; 108: 306-314.

[6] Ren N, Shang X, Wu G and Tian X. Papillary thyroid carcinoma with parapharyngeal and pulmonary metastases: a case report and literature review. Asian J Surg 2024; 47: 1917-1918.

[7] Sima OC, Cucu AP, Terzea D, Nistor C, Vasilescu F, Eftimie LG, Ciobica ML, Costachescu M and Carsote M. Multilayered insights into poorly differentiated, *BRAFV600E*-positive, thyroid carcinoma in a rapidly developing goiter with retrosternal extension: from en "Y" cervicotomy to SPECT/CT-positive lung metastases. Diagnostics (Basel) 2025; 15: 2049.

[8] Halada S, Leftin Dobkin S, Baran JA, Sisko L, Robbins SL, Rapp JB, Young LR and Bauer AJ. Pulmonary injury after radioactive iodine therapy in pediatric papillary thyroid cancer: a case report. Horm Res Paediatr 2024; 97: 477-482.

[9] Feng Y, Huang C, Liu X, Xiao Z, Wang L, Lu Z and Ming J. A bibliometric analysis of inflammation and thyroid carcinoma: research trends and future perspectives. Front Oncol 2025; 15: 1593006.

[10] Banerjee S, Nahar U, Dahiya D, Gupta R, Mukherjee S, Sachdeva N, Sood A, Dey P, Radotra B and Bhansali A. IL-17 A correlates with disease progression in papillary thyroid carcinoma. Diagn Pathol 2023; 18: 93.

[11] Kim JS, Choi M, Kim SH, Hwang HK, Lee WJ and Kang CM. Systemic inflammation response index correlates with survival and predicts oncological outcome of resected pancreatic cancer following neoadjuvant chemotherapy. Pancreatology 2022; 22: 987-993.

[12] Rezazadeh M, Kamyabi A, Pisheh RG, Noroozie S, Amiri BS, Negahi A and Radkhah H. Diagnostic value of peripheral blood inflammatory indices for clinicopathological profile of colorectal cancer: a retrospective observational study. BMC Gastroenterol 2025; 25: 127.

[13] Pang J, Yang M, Li J, Zhong X, Shen X, Chen T and Qian L. Interpretable machine learning model based on the systemic inflammation response index and ultrasound features can predict central lymph node metastasis in cN0T1-T2 papillary thyroid carcinoma. Gland Surg 2023; 12: 1485-1499.

[14] Zanoni DK, Patel SG and Shah JP. Changes in the 8th edition of the American joint committee on cancer (AJCC) staging of head and neck cancer: rationale and implications. Curr Oncol Rep 2019; 21: 52.
[15] Kasprzak A. The role of tumor microenvironment cells in colorectal cancer (CRC) cachexia. Int J Mol Sci 2021; 22: 1565.
[16] Kennel KB, Bozlar M, De Valk AF and Greten FR. Cancer-associated fibroblasts in inflammation and antitumor immunity. Clin Cancer Res 2023; 29: 1009-1016.
[17] Pęczek P, Gajda M, Rutkowski K, Fudalej M, Deptała A and Badowska-Kozakiewicz AM. Cancer-associated inflammation: pathophysiology and clinical significance. J Cancer Res Clin Oncol 2023; 149: 2657-2672.
[18] Ugel S, Canè S, De Sanctis F and Bronte V. Monocytes in the tumor microenvironment. Annu Rev Pathol 2021; 16: 93-122.
[19] Wu Z, Zhang Z and Gu C. Prognostic and clinicopathological impact of systemic inflammation response index (SIRI) on patients with esophageal cancer: a meta-analysis. Syst Rev 2025; 14: 104.
[20] Lu YF, Wu CY, Lo WC, Chiu YL, Shueng PW, Hsieh CH, Hsu CX, Kuo DY, Hou PY and Liao LJ. Postchemoradiotherapy systemic inflammation response index predicts treatment response and overall survival for patients with locally advanced nasopharyngeal cancer. J Formos Med Assoc 2023; 122: 1141-1149.
[21] Gu X, Han X, Shen Y and Shi Y. Prognostic value of systemic inflammation response index in cancer patients treated with PD-1/PD-L1 immune checkpoint inhibitors: a meta-analysis. Ann Med 2024; 56: 2413415.
[22] Zhang S and Cheng T. Prognostic and clinicopathological value of systemic inflammation response index (SIRI) in patients with breast cancer: a meta-analysis. Ann Med 2024; 56: 2337729.
[23] Menyhart O, Fekete JT and Győrffy B. Inflammation and colorectal cancer: a meta-analysis of the prognostic significance of the systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI). Int J Mol Sci 2024; 25: 8441.
[24] Shen H and Zuo F. Prognostic role of systemic inflammation response index (SIRI) in patients with pancreatic cancer: a meta-analysis. Front Oncol 2024; 14: 1465279.
[25] Wu Q and Zhao H. Prognostic and clinicopathological role of pretreatment systemic inflammation response index (SIRI) in gastric cancer: a systematic review and meta-analysis. World J Surg Oncol 2024; 22: 333.
[26] Chen DW, Carr G, Worden FP, Veenstra CM, Haymart MR and Banerjee M. Survival prognostication in patients with differentiated thyroid cancer and distant metastases: a SEER population-based study. Thyroid 2024; 34: 837-845.
[27] Luo L, Xia J, Zhang R and Yao X. Efficacy and prognosis in patients with papillary thyroid cancer with postoperative preablative stimulated thyroglobulin above 10 ng/ml after initial therapy with radioiodine. Acta Endocrinol (Buchar) 2024; 20: 186-192.
[28] Yang LY and Yang LP. The association between composite inflammatory indicators and the clinicopathological characteristics of differentiated thyroid carcinoma. Front Mol Biosci 2025; 12: 1660379.
[29] Refaat L, Eissa MS, Elnaggar GN, Mehesen M, Eissa MS, Kamal A and Abdellateif MS. Systemic inflammatory indices comprising monocytes provide a clinical significance for thyroid cancer identification. Sci Rep 2025; 15: 39967.
[30] Modica R, Minotta R, Liccardi A, Cannavale G, Benevento E and Colao A. Evaluation of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) as potential biomarkers in patients with sporadic medullary thyroid cancer (MTC). J Pers Med 2023; 13: 953.
[31] Cai Y, Zhao L, Zhang Y and Luo D. Association between blood inflammatory indicators and prognosis of papillary thyroid carcinoma: a narrative review. Gland Surg 2024; 13: 1088-1096.
[32] Gu Y, Yu M, Deng J and Lai Y. 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. Int J Gen Med 2024; 17: 2887-2897.