Article

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Characteristics of Lymphatic Metastasis in Young Patients With Thyroid Carcinoma: Immunobiological and Epidemiological Perspectives

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Background: Although cervical lymphatic metastasis (LM) of thyroid carcinoma (TC) occurs most frequently in children, adolescents, and young adults (CAYA), this population exhibits the most favorable prognosis. This study aimed to clarify the characteristics of LM in CAYA TC patients from immunobiological and epidemiological perspectives.

Methods: The collected preoperative clinical data included serum levels of inflammatory and immunobiological markers. The two-tailed *t*-test or the Mann–Whitney U test was used to compare variables. To control the false discovery rate (FDR), the Benjamini-Hochberg procedure was applied. Categorical variables were analyzed with the chi-squared test. Correlations between continuous variables were identified by Spearman analysis. Receiver operating characteristic (ROC) curve analysis and binary logistic regression were performed to evaluate the association of these factors with LM. Bootstrap resampling (1000 replicates) was used to correct for optimism and assess model stability.

Results: This study was ultimately limited to 487 CAYA participants, including 317 (65.1%) with cervical LM. The LM rate was higher in CAYA males (71.9%) than in CAYA females (62.4%) (p = 0.045). Patients with LM exhibited elevated levels of monocyte ratio (MOR) (q = 0.038), thyroglobulin (Tg) (q = 0.008), and tumor necrosis factor-alpha (TNF-α) (q = 0.04) (q-values representing FDR-adjusted p-values). Young age (OR = 0.79, 95% CI: 0.70–0.91, p = 0.001) and larger tumor size (OR = 1.43, 95% CI: 1.05–1.96, p = 0.02) were independent risk factors for LM. The ROC curve revealed that age (area under the curve (AUC) = 0.63, 95% CI: 0.56–0.70), tumor size (AUC = 0.66, 95% CI: 0.59–0.74), Tg (AUC = 0.58, 95% CI: 0.51–0.66), and TNF-α (AUC = 0.61, 95% CI: 0.53–0.68) were predictive of LM. The combination of four indicators (age, tumor size, Tg, and TNF-α) enhanced predictive performance, achieving an AUC of 0.70 (95% CI: 0.63–0.76). In the N1 subgroup, significant sex differences were observed in markers, including Tg, interleukin (IL)-6, IL-4, MOR, natural killer cells, lymphocyte ratio, antithyroglobulin antibody, neutrophil ratio, platelet and Th/Ts (all $q < 0.05$).

Conclusion: This study identified younger age and larger tumor size as independent risk factors for LM in CAYA TC patients, and preoperative immune-inflammatory markers were associated with LM. Additionally, patients with LM displayed distinct sex-specific immune-inflammatory features.

Keywords: thyroid carcinoma; lymphatic metastasis; sex differences; young adults; adolescents; children; biomarkers

Introduction

There are notable sex- and age-related differences among patients with thyroid carcinoma (TC). Although TC occurs more commonly in females, males exhibit more malignant behavior and a poorer prognosis [1]. Most TCs are well-differentiated, particularly among young individuals. Differentiated thyroid carcinoma (DTC) constitutes the majority of TC cases, with papillary thyroid carcinoma (PTC) being the most common type, accounting for approximately 85% of cases [2]. Age is incorporated into the American Joint Committee on Cancer (AJCC) staging system (8th Edition) as an important basis for staging and guiding the diagnosis and treatment of DTC. Young and middle-aged patients (<55 years) are classified as stage I or II, regardless of local extension and regional cervical lymphatic metastasis (LM). Compared to older patients, this younger population demonstrates a more favorable long-term prognosis, with a 5-year survival rate exceeding 95% [3]. Nevertheless, the occurrence of cervical LM is greater in this population [4,5], and tumors often present at a more advanced stage [6].

The prognostic significance of LM in children, adolescents, and young adults (CAYA) remains controversial.

Routine physical examination and screening may contribute to the overdiagnosis and overtreatment of TC in adults. In contrast, neck imaging and thyroid screening are performed less frequently for CAYA [3], which may be associated with larger tumors or cervical LM at the initial diagnosis of TC in these populations. While most studies identify LM as a negative prognostic factor in older patients with PTC and poorly differentiated TC, LM has also been associated with prognosis and overall survival (OS) of young PTC patients [7]. Thus, the interplay among age at diagnosis, LM, and OS warrants further investigation.

Despite exhibiting the highest LM rate, younger TC patients have a favorable prognosis. Conversely, the LM rate is lower for elderly patients, but they have poorer clinical outcomes. The physiological microenvironment varies across different age groups, suggesting that the mechanisms underlying LM may differ between young and elderly patients. Currently, no clear evidence has indicated unique features or mechanisms of LM specific to the young TC patients. To explore preliminary distinctions in LM features, hematological analysis of young cohorts provides a foundation for further mechanistic investigations of age-related differences in the occurrence of LM of TC.

Methods

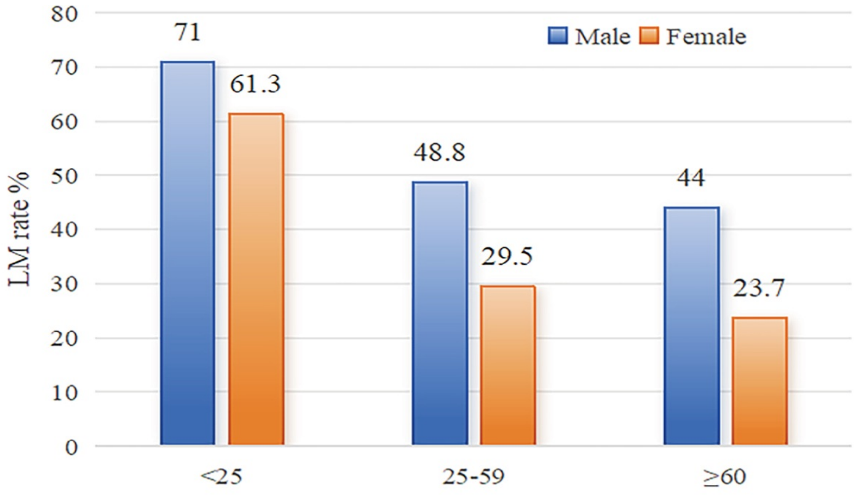
Data Source

Clinical data were retrieved from the medical records of TC patients treated at the Third Affiliated Hospital of Kunming Medical University (Kunming, China). The inclusion criteria included: patients first diagnosed between 2014 and 2023; histologically confirmed TC; and absence of other coexisting malignancies. The exclusion criteria were unclear N staging (reasons for undetermined N staging included: no lymph node biopsy performed at our hospital, fine needle aspiration of suspicious lymph nodes showed no metastasis without subsequent dissection, missing pathological data, or other unspecified reasons), unavailable preoperative clinical data, and the presence of acute co-infection or other clinically significant laboratory abnormalities (such as anemia). Acute co-infection was determined by elevations in all three parameters: white blood cell count (WBC), neutrophil count (NE), and neutrophil ratio (NR) above the upper limits of normal. To enhance data homogeneity, this study was limited to DTC patients, as only 3 cases of medullary thyroid carcinoma (MTC) had complete preoperative clinical information.

Data from blood tests that were conducted within 7 days before surgery included the WBC, NE, NR, lymphocyte count (LYM), lymphocyte ratio (LR), monocyte count (MO), monocyte ratio (MOR), platelet count (PLA), T-cell ratio (TR), CD3+CD4+ T cell ratio (Th), CD3+CD8+ T cell ratio (Ts), Th/Ts, natural killer cell ratio (NK), cytokine-induced killer cell ratio (CIK), and serum levels of interferon-gamma (IFN-γ), tumor necrosis factor α (TNF-α), interleukin (IL)-10, IL-6, IL-4, and IL-2. Thyroglobulin (Tg) level and antithyroglobulin antibody (TgAb) level were measured within 4 weeks before surgery. Demographic and clinicopathological data included age, sex, height, weight, surgical pathology, size of the largest nodule, and LM status (central and lateral cervical lymph nodes). All cases of LM were definitively diagnosed by pathological examination of fine-needle aspiration biopsy specimens or surgically excised lymph nodes. Age criteria in the study are defined based on the MeSH Descriptor Data 2026.

Statistical Analysis

Statistical analysis was conducted with IBM SPSS Statistics for Windows (version 27.0, IBM Corporation, Armonk, NY, USA) and R software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). Figures were generated with Prism 10 software (GraphPad Software, LLC, San Diego, CA, USA) and Origin 24 software (OriginLab Corporation, Northampton, MA, USA). Descriptive statistics were used to analyze patient characteristics by LM status and sex. The Shapiro–Wilk test was applied to determine whether the variables were normally distributed. For normally distributed data, the mean (standard deviation) was the appropriate measure of central tendency, whereas the median (interquartile range, IQR) was preferred for non-normally distributed data. In this study, multiple hematological and cytokine variables were subjected to statistical testing. To control the increased risk of type I error (false positives) arising from these multiple comparisons, all related hypothesis tests (constituting a single family of all tests) were corrected for the false discovery rate (FDR) using the Benjamini–Hochberg procedure. Both the original p-values and the FDR-adjusted p-values (q-values) are reported in the Results section. The two-tailed t-test was used to analyze normally distributed data, and the Mann–Whitney U test was used to compare nonparametric variables between two groups. Categorical variables were analyzed with Pearson's chi-squared test. Binary logistic regression was used to assess the predictive value of clinical indicators for LM. To quantify optimism bias and evaluate the stability of the final logistic regression model, bootstrap internal validation was performed with 1000 replicates. The performance of selected indicators was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC). The combined score was constructed using the predicted probability of LM from a logistic regression model. Correlations between continuous variables were identified by Spearman analysis. A two-sided probability p-value and q-value $<$ 0.05 were considered statistically significant.



	N0	N1	N0	N1	N0	N1
	<25		25-59		≥60	
Male	42	103	1503	1431	141	111
Female	145	230	8083	3383	640	199

Fig. 1. LM rates of different age and sex groups. LM, lymphatic metastasis.

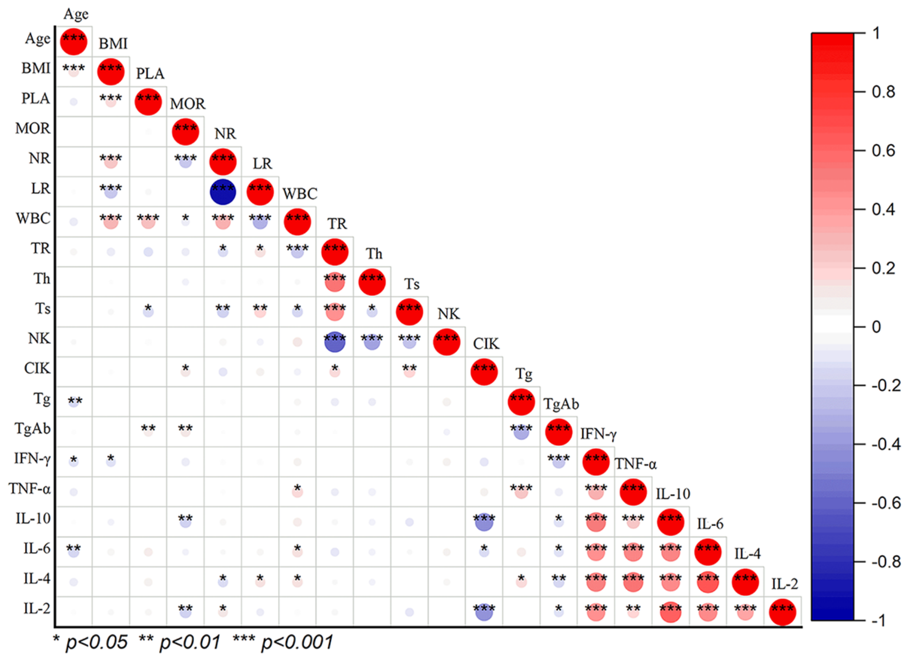


Fig. 2. Correlation analysis among various indicators.

Results

Demographic Characteristics and LM Distribution Trends

A total of 18,601 patients with TC received treatment at our institution over the past decade. After excluding patients with unclear N staging, 16,011 TC cases were included for analysis. Among these, 3331 (20.8%) were male, while 12,680 (79.2%) were female. The cases were further stratified into three age groups: CAYA (<25 years), middle-aged (25–59 years), and elderly (≥60 years). Within the entire cohort, only 520 (3.2%) cases were CAYA. The middle-aged group accounted for the largest proportion of patients (90%), whereas 1091 (6.8%) were

Table 1. Demographic characteristics and sex differences of CAYA TC patients.

	Total (n = 487)	Female (n = 348)	Male (n = 139)	Chi-square	*p*-value
Age				1.37	0.242
≤18	73 (15.0%)	48 (13.8%)	25 (18.0%)		
19–24	414 (85.0%)	300 (86.2%)	114 (82.0%)		
BMI				17.39	<0.001
<18.5	92 (18.9%)	76 (21.9%)	16 (11.5%)		
18.5–25	300 (61.6%)	219 (62.9%)	81 (58.3%)		
>25	95 (19.5%)	53 (15.2%)	42 (30.2%)		
T Stage				2.64	0.115
T1–T2	371 (76.2%)	272 (78.2%)	99 (71.2%)		
T3–T4	116 (23.8%)	76 (21.8%)	40 (28.8%)		
N Stage				4.02	0.045
N0	170 (34.9%)	131 (37.6%)	39 (28.1%)		
N1	317 (65.1%)	217 (62.4%)	100 (71.9%)		
M Stage				0.01	0.936
M0	470 (96.5%)	336 (96.6%)	134 (96.4%)		
M1	17 (3.5%)	12 (3.4%)	5 (3.6%)		
co-HT				5.00	0.025
Yes	29 (6.0%)	26 (7.5%)	3 (2.2%)		
No	458 (94.0%)	322 (92.5%)	136 (97.8%)		

CAYA, children, adolescents, and young adults; TC, thyroid carcinoma; BMI, body mass index; HT, Hashimoto's Thyroiditis.

elderly. Across all three age groups, the prevalence of LM was higher in males than in females and showed a decreasing trend with increasing age (Fig. 1).

Among the 520 CAYA patients, 487 (348 [71.5%] females and 139 [28.5%] males) were ultimately included in this study, including 8 children (age, 6–12 years), 65 adolescents (age, 13–18 years), and 414 young adults (age, 19–24 years). Notably, 85.0% of the cohort was aged 19–24 years, with a median age of 22 years, while 19.5% were overweight or obese (body mass index [BMI] >25) and 18.9% were underweight (BMI <18.5). Furthermore, 371 (76.2%) patients were diagnosed with stage T1 or T2, and 317 (65.1%) with cervical LM. Only 17 patients presented with distant metastasis, all involving the lungs. Hashimoto thyroiditis (HT) was identified in 29 patients (Table 1). There were no significant differences in age distribution, T stage and M stage between male and female CAYA patients. However, males exhibited a higher rate of LM and a greater prevalence of overweight and obese, whereas TC coexisting with HT was more common in females (Table 1). There was no TC-related death in this cohort during the follow-up period (7–110 months).

Distribution Characteristics of Immune-Inflammatory Markers Based on LM Status

To elucidate the characteristics of LM in CAYA TC patients, common inflammatory and immune indicators were analyzed. The 487 TC patients were divided into two groups (N0 and N1) based on LM status. Patients with LM were younger (q = 0.010), had larger primary tumors (q = 0.008), and had higher levels of MOR (q = 0.038), Tg (q = 0.008), and TNF-α (q = 0.040). Notably, MO, LYM, NE, LR, NR, PLA, WBC, Th, Ts, NK, CIK, IFN-γ, IL-2, IL-6, IL-4 and IL-10 showed no statistically significant differences after FDR correction (Table 2).

There were complex correlations between inflammatory and immunobiological markers (Fig. 2). In the aforementioned univariate analysis, it was found that patients with LM were relatively younger. Analysis of the relationship of age with these inflammatory and immunobiological markers revealed a significant but weak negative correlation (Fig. 2) of age with serum levels of Tg (p = 0.001, r = –0.2), IL-6 (p = 0.008, r = –0.2) and IFN-γ (p = 0.046, r = –0.15).

Young Age and Larger Tumor Size Were Independent Risk Factors for LM

We incorporated the five statistically significant indicators (age, tumor size, TNF-α, Tg and MOR) from the univariate analysis into the binary logistic regression analysis. Multicollinearity diagnostics confirmed the absence of significant collinearity among the five predictors entered into the logistic regression model, with all variance inflation factor values ranging between 1.0 and 2.0. Hosmer-Lemeshow test (χ^2 = 7.7, df = 8, p = 0.46) indicated a good model fit between the model-predicted probabilities and the observed outcomes. The results showed that young age (OR = 0.79, 95% CI: 0.70–0.91, p = 0.001) and larger tumor size (OR = 1.43, 95% CI: 1.05–1.96, p = 0.02) were independent risk factors for LM in CAYA TC patients, with age having the

Table 2. Inflammatory and immunobiological indicators of CAYA TC patients based on LM status.

	N0 (n = 170)	N1 (n = 317)	Statistics	*p*-value	*q*-value
Age (year)	23 (21.00, 24.00)	22 (19.00, 23.00)	z = –3.20	0.001	0.010
BMI	21.10 (19.04, 24.67)	21.09 (18.81, 23.61)	z = –1.35	0.171	0.327
Tumor size (cm)	1.00 (0.50, 1.50)	1.40 (0.80, 2.50)	z = 6.87	<0.001	0.008
NR (%)	54.95 ± 8.30#	54.10 ± 8.87#	t = –1.02	0.310	0.471
LR (%)	36.65 ± 7.94#	37.06 ± 7.99#	t = 0.55	0.590	0.670
Th (%)	34.38 ± 8.03#	34.89 ± 7.59#	t = 0.48	0.634	0.684
Ts (%)	23.83 ± 6.46#	25.54 ± 6.16#	t = 1.98	0.050	0.138
PLA (10^9/L)	269.00 (220.00, 311.00)	260.00 (217.50, 310.80)	z = –0.17	0.862	0.860
MO (10^9/L)	0.33 (0.26, 0.40)	0.36 (0.28, 0.48)	z = 2.44	0.015	0.063
MOR (%)	5.20 (4.40, 6.30)	5.50 (4.60, 7.00)	z = 2.75	0.006	0.038
NE (10^9/L)	3.27 (2.73, 4.44)	3.51 (2.64, 4.39)	z = 0.18	0.860	0.860
LYM (10^9/L)	2.14 (1.85, 2.67)	2.40 (1.89, 2.99)	z = 1.09	0.282	0.466
WBC (10^9/L)	6.05 (5.31, 7.48)	6.41 (5.32, 7.91)	z = 1.23	0.223	0.393
TR (%)	69.15 (64.40, 75.30)	69.50 (63.80, 76.80)	z = 0.63	0.531	0.663
Th/Ts	1.50 (1.10, 1.89)	1.41 (1.10, 1.70)	z = –0.99	0.322	0.471
NK (%)	16.50 (11.80, 22.50)	15.60 (10.90, 23.40)	z = –0.78	0.436	0.572
CIK (%)	1.10 (0.50, 2.50)	1.80 (0.60, 4.53)	z = 1.86	0.064	0.150
Tg (ng/mL)	14.37 (6.55, 61.85)	28.59 (7.13, 114.85)	z = 3.81	<0.001	0.008
TgAb (IU/mL)	12.27 (10.00, 85.89)	16.51 (10.31, 64.41)	z = 2.17	0.030	0.107
IFN-γ (pg/mL)	56.00 (31.90, 73.60)	59.99 (39.38, 88.65)	z = 1.41	0.160	0.327
TNF-α (pg/mL)	29.50 (23.40, 35.20)	32.80 (27.55, 41.25)	z = 2.65	0.008	0.040
IL-10 (pg/mL)	16.29 (10.30, 30.40)	16.10 (10.40, 25.50)	z = –0.55	0.581	0.671
IL-6 (pg/mL)	15.70 (11.50, 21.40)	15.80 (11.20, 26.10)	z = 0.94	0.346	0.486
IL-4 (pg/mL)	27.80 (19.50, 35.10)	30.90 (23.30, 37.10)	z = 2.00	0.046	0.138
IL-2 (pg/mL)	28.80 (20.10, 44.90)	21.70 (18.89, 40.45)	z = –1.67	0.092	0.201

#: Data that followed a normal distribution are expressed as mean ± standard deviation and were compared using the *t*-test. Otherwise, they are presented as median (IQR) and compared using the Mann-Whitney U test. The *p*-value adjustment was performed using FDR control via the Benjamini–Hochberg method. PLA, platelet count; MO, monocyte count; MOR, monocyte ratio; NE, neutrophil count; NR, neutrophil ratio; LYM, lymphocyte count; LR, lymphocyte ratio; WBC, white blood cell count; TR, T-cell ratio; Th, CD3+CD4+ T cell ratio; Ts, CD3+CD8+ T cell ratio; LM, lymphatic metastasis; NK, natural killer cell ratio; CIK, cytokine-induced killer cell ratio; Tg, Thyroglobulin; TgAb, Antithyroglobulin antibody; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor α; IL, interleukin.

most significant impact (Fig. 3). Serum levels of Tg, TNF-α and MOR were not significant risk factors for LM.

Bootstrap validation confirmed the stability of the key predictors identified in the original model. The Brier score increased slightly from 0.202 to 0.212 after optimism correction (bootstrap 95% CI: 0.203–0.215), suggesting acceptable prediction error. Calibration curves demonstrated good agreement between predicted probabilities and observed event rates. Age (bootstrap median OR = 0.80, 95% CI: 0.70–0.88) and tumor size (bootstrap median OR = 1.45, 95% CI: 1.10–2.12) remained consistently significant across bootstrap samples.

Age, Tumor Size, TNF-α and Tg Levels Were Associated With LM

An ROC curve (Table 3) was plotted for the five statistically significant indicators (*q*-value $<$ 0.05 in Table 2) between the N0 and N1 groups. The optimal cut-off value was determined by maximizing Youden's index (sensitivity + specificity − 1). This curve was used to evaluate the sensitivity and specificity of these indicators to predict LM in CAYA TC patients. The results demonstrated that age (p = 0.001, AUC = 0.63, 95% CI: 0.56–0.70), tumor size ($p < 0.001$, AUC = 0.66, 95% CI: 0.59–0.74), Tg (p = 0.041, AUC = 0.58, 95% CI: 0.51–0.66), and TNF-α (p = 0.008, AUC = 0.61, 95% CI: 0.53–0.68) were predictive of LM in CAYA TC patients. The optimal cut-off values were 20.50, 0.75, 19.88, and 29.75, respectively. Notably, the combination of four indicators (age, tumor size, Tg, and TNF-α) demonstrated greater discriminative capacity than any single variable, achieving an AUC of 0.70 (95% CI: 0.63–0.76). The combination of these four indicators represents a meaningful integration of clinical and serum markers. Its overall performance serves as a significant, though not deterministic, exploratory predictor of LM in CAYA TC patients.

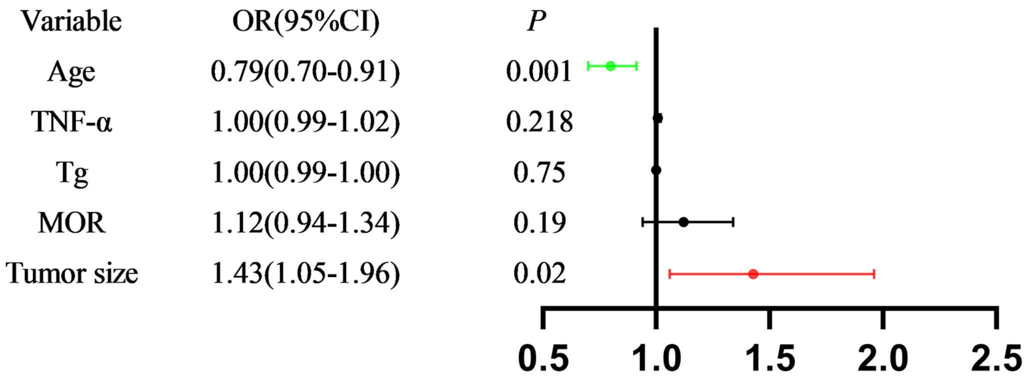


Fig. 3. Binary logistic regression showed that young age and larger tumor size were independent risk factors for LM of CAYA TC patients.

Table 3. Optimal cut-off values for inflammatory and immunobiological indicators based on the Youden's index of the ROC curve.

Index	AUC (95% CI)	*p*	The optimal cut-off value	Sensitivity	Specificity	Youden's
Tumor size	0.66 (0.59–0.74)	<0.001	0.75	0.85	0.40	0.25
Tg	0.58 (0.51–0.66)	0.041	19.88	0.60	0.62	0.22
Age	0.63 (0.56–0.70)	0.001	20.50	0.86	0.36	0.22
MOR	0.56 (0.48–0.63)	0.170	5.25	0.60	0.51	0.11
TNF-α	0.61 (0.53–0.68)	0.008	29.75	0.68	0.54	0.22
Combined^{c}	0.70 (0.63–0.76)	<0.001	0.56	0.73	0.55	0.28

c: Combining the above four statistically significant indicators (tumor size, Tg, age, and TNF-α) had the best performance for LM in CAYA TC patients. Predicted probability cut-off value is 0.56. MOR, monocyte ratio; Tg, Thyroglobulin; TNF-α, tumor necrosis factor α.

Differences in Immune-Inflammatory Characteristics of CAYA Male and Female TC Patients With LM

The occurrence of LM was higher in CAYA males than in females. Therefore, separate analyses were conducted (Table 4). Further stratified analysis of patients with LM (N1 group) revealed a distinct sex-specific immune-inflammatory profile. CAYA females with LM exhibited significantly higher levels of TgAb (q = 0.004), NR (q = 0.004), PLA (q = 0.004), and Th/Ts ratio (q = 0.015), alongside lower levels of MOR (q = 0.015), LR (q = 0.017), NK (q = 0.01), Tg (q = 0.004), IL-6 (q = 0.017), and IL-4 (q = 0.011) compared to CAYA males. However, the levels of WBC, TR, CIK, IFN-γ, TNF-α, IL-10, and IL-2 showed no significant differences.

To further explore the sex-based differences in the distribution of inflammatory immune markers among N1 patients, we integrated the findings from the analyses described above (Table 5). The analysis indicates that female patients manifested as a helper-immunity-biased adaptive response (elevated Th/Ts ratio), a pronounced thyroid-specific autoimmune background (elevated TgAb), and a systemic pro-inflammatory state (elevated NR and platelets). In contrast, male patients demonstrated a profile towards cellular cytotoxicity (elevated LR and NK cell levels), a prominent tumor-derived antigen signal (high Tg), and significant mobilization of the monocyte-macrophage lineage (elevated MOR). Therefore, these differential immunological and inflammatory profiles offer insights for future investigations into the distinct sex-based differences in TC.

Discussion

The combined evaluation of blood inflammatory and immune markers helps differentiate benign from malignant thyroid nodules [8–10], and is also an important factor affecting the malignant behavior [11–13] and prognosis [14] of TC. While previous studies have often focused on individual cell counts or simple ratios, our study provided a more comprehensive and integrated view by analyzing a broad panel of cytokines and immune cell subsets within a unique CAYA cohort. This approach unveiled distinct sex-specific immune-inflammatory features associated with LM, a finding that may help explain the epidemiological observation of higher LM rates in the young population.

A higher neutrophil-to-lymphocyte ratio (NLR) is reportedly directly correlated with an increased risk of developing cancer in adults [15], and the NLR has shown great potential to predict benign and malignant thyroid tumors [16], as well as LM [17]. The NLR is also predictive of a poorer prognosis of radioiodine-refractory TC [18]. In

Table 4. Differences in inflammatory and immunobiological indices between CAYA male and female patients with LM (descriptive comparison limited to the N1 subgroup).

Index	N1 (317)				
	Male (n = 100)	Female (n = 217)	Statistics	p-value	q-value
NR	51.45 ± 8.97#	55.34 ± 8.57#	t = 3.70	<0.001	0.004
LR	38.77 ± 8.54#	36.27 ± 7.62#	t = –2.60	0.009	0.017
PLA	237.50 (202.00, 305.50)	279.50 (226.00, 312.25)	z = 3.30	<0.001	0.004
MOR	6.00 (4.98, 7.25)	5.35 (4.50, 6.97)	z = –2.70	0.007	0.015
WBC	6.41 (5.29, 7.69)	6.32 (5.34, 8.09)	z = –0.15	0.880	0.880
TR	68.30 (61.28, 76.18)	70.50 (63.88, 76.98)	z = 1.29	0.200	0.288
Th/Ts	1.24 (0.87, 1.60)	1.50 (1.21, 1.80)	z = 2.70	0.007	0.015
NK	18.50 (12.08, 28.43)	14.50 (10.08, 19.98)	z = –2.94	0.003	0.010
CIK	1.55 (0.25, 4.90)	1.80 (0.70, 4.38)	z = 0.54	0.590	0.680
Tg	78.10 (20.52, 393.93)	19.94 (4.07, 76.55)	z = –4.57	<0.001	0.004
TgAb	14.78 (10.14, 22.05)	20.99 (10.38, 127.00)	z = 3.75	<0.001	0.004
IFN-γ	63.75 (33.70, 102.28)	56.20 (39.80, 84.38)	z = –0.58	0.562	0.670
TNF-α	34.50 (27.55, 48.43)	31.80 (27.03, 39.63)	z = –1.19	0.230	0.322
IL-10	16.95 (10.48, 31.08)	14.95 (10.40, 23.30)	z = –1.14	0.252	0.330
IL-6	21.15 (12.85, 31.65)	13.90 (11.00, 22.48)	z = –2.60	0.009	0.017
IL-4	35.10 (26.08, 45.33)	28.45 (21.73, 34.85)	z = –2.86	0.004	0.011
IL-2	23.75 (18.38, 43.95)	21.60 (19.50, 37.23)	z = –0.18	0.860	0.877

#: Data that were normally distributed. PLA, platelet count; MOR, monocyte ratio; NR, neutrophil ratio; LR, lymphocyte ratio; WBC, white blood cell count; TR, T-cell ratio; Th, CD3+CD4+ T cell ratio; Ts, CD3+CD8+ T cell ratio; NK, natural killer cell ratio; CIK, cytokine-induced killer cell ratio; Tg, Thyroglobulin; TgAb, Antithyroglobulin antibody; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor α; IL, interleukin.

Table 5. Sex-based differences in immune-inflammatory features among CAYA TC patients with LM.

Immune feature	Pattern in female patients	Pattern in male patients	Core biological difference
Adaptive Immunity	↑ Th/Ts (CD4+ T cell dominance, CD8+ T cell suppression)	↑ LR (enhanced cellular immunity)	Females: Helper immunity bias Males: Cellular immunity bias
Thyroid-Specific Response	↑ TgAb (strong autoimmune response)	↑ Tg (high tumor burden/secretion)	Females: Pronounced autoimmune background Males: Prominent tumor-derived antigen signal
Innate Immunity	↑ NR & ↑ Platelets (chronic, systemic inflammation)	↑ MOR & ↑ NK cells (abundant macrophage precursors, enhanced cytotoxicity)	Females: Systemic pro-inflammatory state Granulocyte-predominant Males: Monocyte/macrophage-lineage mobilization

↑: Significantly higher level in the indicated sex group (N1 subgroup, $q < 0.05$; as detailed in Table 4).

addition, other indices, such as the platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), are reportedly predictive of adverse clinical features of TC patients [19,20]. The PLR was associated with disease-free status and has been reported to be higher in DTC patients with distant metastasis and persistent disease, as well as associated with disease-related death, while the LMR is a risk factor for active disease [21]. However, the results of previous studies are sometimes contradictory [22], likely due to differences in age groups and the proportions of males versus females [14]. For instance, age and HT have been reported to influence the NLR in females [19].

The age groups of most studies are based on the AJCC staging system, with an age cut-off of 55 years. A previous study reported that the mean NLR and PLR were higher in TC patients aged ≤55 years, while there were no significant differences in NE and LYM [23]. However, using 55 years as the age threshold cannot account for the characteristics of younger individuals. The present study focused on younger patients (age <25 years) and identified sex differences by combining analyses of routine blood indicators, common cytokines, and immune cells to explore the characteristics of LM in the CAYA population. However, since there are complex correlations and crosstalk among these indicators, evaluation of any individual marker requires a holistic and comprehensive approach. We hypothesize that, in CAYA patients, a vigorous immune surveillance system may be actively engaged, detecting and responding to disseminating tumor cells. This heightened immune activity could paradoxically correlate with a higher detectable rate of LM, due to immune cell trafficking and lymph node activation, while simultaneously providing a protective effect that contributes to the excellent long-term prognosis characteristic of this age group. Therefore, the prognostic implication of LM and its associated immune markers appears to be fundamentally age-dependent.

Monocytes contribute to tumor development by differentiating into tumor-associated macrophages (TAMs), which are recruited to tumors via chemotactic signals from cancer cells [24]. Therefore, both the count and percentage of monocytes may reflect the abundance of TAMs, which in turn indicates tumor burden. Increased monocyte level is associated with poor prognosis in multiple malignancies [25,26], consistent with the results of the present study. As a promoter of M2 macrophage polarization, IL-4 may participate in the formation of the tumor microenvironment, thereby promoting LM, especially in individuals with higher monocyte levels. This suggests a potential synergy where a higher monocyte reservoir skewed towards an M2 phenotype by factors, such as IL-4, may foster a tumor microenvironment conducive to lymphatic spread in young males. TNF-α was also elevated in the overall N1 group. TNF-α has been implicated in the proliferation and differentiation of B cells under steady-state conditions and has also been associated with the pathogenesis of various cancers. The carcinogenic effects of TNF-α are mediated through activation of the pro-inflammatory transcription factor NF-κB. Notably, some tumor cells exhibit an "addiction" to NF-κB, rendering them more dependent on TNF-α [27]. Although elevated TNF-α is not an independent risk factor for LM, its increase in the N1 subgroup suggests that CAYA patients with LM may be in a distinct state of inflammatory activation.

The profiles summarized in Table 5 revealed distinct immune-inflammatory characteristics: CAYA females with LM exhibited signs of a systemic, humoral/autoimmune-biased response (elevated Th/Ts, TgAb, platelets, and neutrophil-driven inflammation), while CAYA males were characterized by a focused, cellular/innate pro-tumor response (elevated cytotoxicity markers, Tg, IL-6, and monocyte mobilization). In males, the prominence of Tg (indicative of tumor burden and differentiation) and IL-6 suggested a tumor-driven microenvironment. IL-6 is a multi-effector cytokine mainly produced by monocyte macrophages, lymphoid cells, T cells, B cells, granulocytes, mast cells, and endothelial cells [28]. IL-6 is an important trigger of JAK/STAT signaling [29], which regulates the malignant behavior of tumors. Similarly, growth hormone (GH), an age-driven hormone, typically acts through JAK/STAT signaling. Stimulation of endogenous GH and IL-6 receptors selectively activates different JAKs and STATs [30]. The specific elevation in CAYA males is noteworthy and may intersect with age-related hormonal axes. These findings suggest that the hormonal milieu of young males, characterized by high GH and androgen levels, may interact with IL-6 to uniquely shape a tumor-promoting environment. Estrogen and its receptors also contribute to the distinctive tumor secretory profile and the "highly inflammatory" microenvironment characteristic in females [31].

TC patients have relatively higher levels of Tg and TNF-α [32], with serum Tg being the most sensitive and specific marker of DTC. In PTC, the importance of Tg and TgAb to predict LM has been recognized [33]. Similarly, the results of the present study showed that Tg levels may be associated with LM of TC patients, and CAYA males had higher Tg levels than CAYA females. A Tg level above 19.88 ng/mL was not significant for clinical diagnosis, but it may be related to a larger tumor burden in highly differentiated TC. Cheong *et al*. [34] suggested that while benign thyroid nodules were larger than malignant ones, the NLR was a significant predictor of TC only in nodules larger than 2 cm, not in smaller ones. In our study, the median tumor size was 1 (N0 group)–1.4 (N1 group) cm in CAYA TC. For suspected thyroid nodules, clinicians should consider a higher index of suspicion for malignancy in these patients with tumor sizes 1–1.5 cm and younger than 20 years, especially for those with higher Tg levels.

Studies focusing on the unique characteristics of CAYA TC patients remain scarce. Unlike previous studies, our findings revealed that higher NE and lower LYM were not associated with an increased risk of LM, especially for CAYA male patients with LM, who had higher LYM. Although the roles of lymphocytes remain controversial [14], most studies have suggested that low LYM is associated with a poor prognosis. However, a study suggested that high LYM could be associated with the malignant behavior of cancers [14]. Children and adolescents with PTC and relatively higher levels of proliferating lymphocytes reportedly have the best prognosis, as CD8+ lymphocytes or the combination of CD4+, CD8+, and CD19+ lymphocytes were associated with a lower risk of disease recurrence [35]. Meanwhile, Gupta *et al*. [36] demonstrated that proliferation of tumor-associated lymphocytes is associated with improved disease-free survival for young patients with TC, and the number of proliferating lymphocytes was greatest for PTC with regional lymph node involvement. CAYA patients have more vigorous metabolism and immune responses, suggesting a potential connection between increased lymphocyte levels and a greater LM rate. Immune surveillance in younger TC patients may detect the "escape" of tumor cells, triggering a rapid immune response that changes the number and function of related immune cells. The levels of peripheral blood lymphocytes and monocytes may represent changes to the populations of active cells. In addition, certain factors in CAYA TC patients may induce "lymph node homing" of tumor cells and increase the infiltration of tumor-associated lymphocytes. This phenomenon may be amplified in patients with high tumor-associated lymphocyte levels. Therefore, the higher rate of LM did not affect the good prognosis of younger TC patients.

Some limitations to this study must be addressed. CAYA patients represent a small subset of the overall TC population. This study provides an exploratory description focused on this specific patient subgroup; therefore, the findings may have limited generalizability and stability when applied to the broader TC patient population. In addition, our findings may not reflect the clinical characteristics of young patients with MTC and anaplastic thyroid carcinoma. Moreover, the cohort was predominantly aged between 18 and 24 years, which may not adequately represent younger children and adolescents. The small sample size may have further increased the variability and potential bias, particularly among young males. Immune-inflammatory marker profiling was conducted only in the CAYA subgroup, without comparisons across the full age range, limiting the generalizability of these findings beyond this single-center young population. As a retrospective single-center study, causal relationships between indicators and LM cannot be established, nor can the findings be assumed to represent populations of different regions and ethnicities. Therefore, we can only provide a preliminary and exploratory explanation for the observed association between immune-inflammatory markers and LM. During the follow-up period, accurately capturing disease recurrence and time was challenging. Our assessment was limited to OS, which confirms that the high incidence of LM did not significantly increase TC-related mortality within this group. The selection of indicators was based on previous cases, precluding comprehensive validation of inflammatory and immune markers. These indicators exhibited substantial heterogeneity across individuals, influenced by a range of factors, such as infections and autoimmune disorders, resulting in low specificity. This study primarily reported unadjusted between-group comparisons to describe the overall sex-based distribution differences of immune markers, reflecting the combined effect of multiple real-world factors. Combining multiple indicators with other clinical methods is necessary to improve the prediction of LM in TC. This study aims to characterize sex-based differences in immune-inflammatory markers and to investigate their correlation with LM in a real-world setting. It should be noted that the defined inclusion and exclusion criteria could introduce potential selection bias, including the exclusion of 13.9% of patients due to undetermined N staging, which led to an inevitable discrepancy between the reported LM rate and the true LM rate and affected the distribution of immune-inflammatory markers. While this could affect the precise estimation of absolute LM rates, the distribution of LM rates across age groups in our study remains consistent with published literature, suggesting that the bias is unlikely to be directional or to fundamentally alter the comparative analyses between age cohorts that are central to our hypothesis. As an exploratory study focused on the immune-inflammatory patterns, our primary goal was to generate hypotheses rather than to provide definitive epidemiological estimates. Therefore, these findings underscore the critical need for future prospective studies with standardized protocols to validate our findings and elucidate the relationship among age, N stage, and immune-inflammatory profiles.

Conclusion

In summary, this study provides an exploratory description of LM characteristics in CAYA TC patients from an immune-inflammatory perspective. Preoperative immune-inflammatory markers were associated with LM, and younger age and larger tumor size were independent risk factors for LM in this population. Furthermore, we extend beyond simple ratios to describe integrated immune-inflammatory features that differ fundamentally by sex: a systemic-inflammatory phenotype in females versus a tumor-focused phenotype in males. These sex-specific profiles are potentially shaped by the unique hormonal and metabolic milieu of young individuals.

Availability of Data and Materials

The data can be obtained by contacting the corresponding author.

Author Contributions

LC, JT and CS designed the study; CS reviewed and revised the paper, and made substantial contributions to conception; LC, TX, and QL collected and organized the clinical data; LC, JT, TX and QL were involved in statistical analysis and graphing. LC drafted the original manuscript. All authors were involved in the critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the STROBE statement. The study protocol was approved by the Institutional Review Board of the Third Affiliated Hospital of Kunming Medical University (approval no. KYLX2024-301) and conducted in accordance with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. The Ethics Committee waived the requirement for informed consent because this retrospective study used anonymized/de-identified data. All reasonable efforts were made to ensure patient anonymity.

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Conflict of Interest

The authors declare no conflict of interest.

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