Association between different regional lymph node metastases of papillary thyroid carcinoma in adolescents and young adults

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Abstract. Adolescents and young adults (AYA) describe the demographic aged between 15-39 years diagnosed with cancer. This group is particularly at risk of papillary thyroid carcinoma (PTC) with a greater severity compared with other ages. Through comparative design, the present study aimed to quantify central lymph node metastasis (CLNM) risk in AYAs. A total of 463 AYA patients with PTC and 489 patients >39 years old with PTC from Ningbo Medical Center Lihuili Hospital (Ningbo, China) were enrolled. Details such as demographic data, serum indices and fine-needle aspiration from the Electronic Medical Records System were extracted and analyzed. AYA patients had significantly higher rates of ipsilateral Hashimoto thyroiditis, thyroid capsular invasion (TCI), CLNM, larger tumors and more positive central lymph nodes (CLN). Independent risk factors of CLNM in AYA patients were as follows: Male sex, presence of TCI, multifocality, bilateral disease and maximum tumor diameter (MTD) ≥1.0 cm. Independent risk factors of lateral lymph node metastasis in AYAs with CLNM were as follows: MTD ≥1.0 cm, maximum diameter of positive CLN ≥1.0 cm, and presence of ipsilateral nodular goiter. Furthermore, AYA patients with PTC displayed significantly greater aggression in primary tumor invasion and neck lymph node metastasis. Based on these findings, a treatment stratification chart was created to guide the PTC treatment approach for AYAs. The present study is registered at the Chinese Clinical Trials Registry (trial registration no. ChiCTR2200064921) in November 2022.

Introduction

Adolescents and young adults (AYAs) describes patients with cancer aged 15-39 years, according to the National Cancer Institute (1) and >1.2 million AYA patients with cancer are newly diagnosed each year globally (2). An increasing body of evidence has reported that the molecular biology of tumors in AYAs is unique compared with that in other ages (3,4). In the case of papillary thyroid carcinoma (PTC), more advanced tumor stages as well as different treatment resistance behaviors are observed when compared with several other cancers such as melanoma, breast cancer and colorectal cancer (5).

Thyroid cancer has one of the highest incidences within endocrine malignancies at 10.1 per 100,000 women and 3.1 per 100,000 men globally (6), with ~80% of thyroid cancers classified as PTC (7). Thus, PTC is one of the primary drivers behind the increase in overall incidence of cancer in AYA, making PTC a valuable topic for study (8). To date, a consensus has not been reached on whether prophylactic central neck dissection should be performed (9), and investigations into this topic may fuel optimal PTC treatment decisions that may greatly benefit AYA patients.

In light of studies that have reported notably different clinical and molecular features in the AYA group of patients with PTC (10,11), the present study compared the clinicopathological characteristics between AYA and older adult patients with PTC. Furthermore, considering that no existing literature has measured neck involvement risk quantitatively for AYA patients with PTC, to the best of our knowledge, the present research predicted and stratified the risk of central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM) for AYA patients to guide individual management strategies of neck regions.

Materials and methods

Patient recruitment. Medical records of 989 patients with confirmed PTC treated surgically at Ningbo Medical Center Lihuili Hospital (Ningbo, China) between 2019 and 2022 were retrospectively analyzed. The inclusion criteria were as follows: i) Aged >15 years; ii) diagnosis of PTC; iii) biopsy performed; iv) surgical treatment received as the only treatment; and v) no distant metastasis. Exclusion criteria were as follows: i) PTC not histologically proven. Several were poorly differentiated thyroid cancer or anaplastic thyroid cancer (n=24); ii) missing clinical or pathological data (n=9); and iii) other head or neck cancers present (n=4). Post-exclusion, 952 patients with diagnosed PTC who underwent thyroidectomy were analyzed.

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Surgical procedure, CLNM and LLNM, and follow-up. From the Electronic Medical Records System, demographic data, serum indices and fine-needle aspiration (FNA) details were collected for analysis. All patients underwent either a total thyroidectomy or thyroid lobectomy with blood drawn and tested prior to procedure. Furthermore, all patients underwent comprehensive whole-body imaging to rule out distant metastasis pre-operation. Central lymph node dissection (CLND) was standard for both treatment and prevention, with positive results confirmed by ≥2 expert pathologists. Lateral lymph node dissection was reserved for patients with suspected lateral neck involvement either preoperatively via ultrasonography or FNA or based on surgical judgment. If post-surgery ultrasonography or FNA within 6 months revealed LLNM in patients who only had CLND, they were retroactively classified as having had lateral neck involvement during their initial surgery. Postoperative pathology was consistently reported using standardized methods within 7 working days following surgery, and for follow-up, each patient underwent a neck ultrasound at 6 months post-surgery, along with other necessary imaging assessments to evaluate postoperative neck conditions. All observed metastatic lymph nodes were ipsilateral.

Statistical analysis. Pearson's χ^2 and the independent t-test were used for the analysis of categorical and continuous variables, respectively. Logistic uni- and multivariate regression analyses were conducted to screen out independent risk factors of CLNM and LLNM in AYA, which were further used to create a nomogram. All aforementioned statistical analyses were performed using SPSS (version 24.0; IBM Corp.). P<0.05 was considered to indicate a statistically significant difference. The performance of these models was assessed using the concordance index (C-index), receiver operating characteristic (ROC) curve and calibration curve. These assessments were performed using R software (version 3.5.1; R Core Team).

Results

Basic demographics and clinicopathological features of patients with PTC within different age groups. Of the 952 patients with PTC, 463 (48.6%) aged 15-39 years were in the AYA group, whilst 489 (51.4%) aged >39 years were in the older adult group. Basic clinical data for both groups is presented in Table I. Significant differences between groups were observed in primary tumor and cervical areas. Compared with the older adult group, the AYA group had significantly larger tumor sizes (0.98±0.80 cm vs. 0.8±0.63 cm; P<0.001), and significantly higher rates of ipsilateral Hashimoto thyroiditis (23.1% vs. 18.0%; P=0.028) and thyroid capsular invasion (TCI; 43.0% vs. 33.1%; P=0.001). However, ipsilateral nodular goiter (iNG) was significantly less prevalent in the AYA group compared with the older adult group (24.6% vs. 33.2%, P=0.006). Furthermore, AYA patients had significantly higher rates of both CLNM (61.8% vs. 35.0%; P<0.001) and LLNM (28.3% vs. 18.7%; P=0.009), with significantly larger positive central lymph node (CLN) sizes and counts (P=0.034 and P<0.001, respectively), in comparison with the older adult group.

AYA patients were further split into two subgroups: 15-29 years (younger AYA group) and 30-39 years (older AYA group). Only tumor size differed significantly between the groups, with a greater maximum tumor diameter (MTD) observed in the younger subgroup compared with that in the older subgroup (1.09±0.96 cm vs. 0.92±0.69 cm; P=0.025), as shown in Table I.

Different clinicopathological features between patients with or without CLNM or LLNM in the AYA group. Out of the 463 AYA patients, 286 (61.8%) had central neck involvement and 81 (17.5%) had lateral neck involvement. When comparing AYA patients based on central involvement, 43.4% of those with CLNM were male, significantly higher than those without CLNM (P=0.004, Table II). Those with CLNM also had significantly larger tumors (1.13±0.86 cm vs. 0.73±0.61 cm; P<0.001) and significantly exhibited factors like TCI (P<0.001), bilateral disease (P<0.001), multifocality (P<0.001) and iNG (P=0.033) more frequently, compared with AYA patients without CLNM.

Among the 286 AYA patients with positive CLNM, differences were analyzed based on LLNM presence. Those with positive LLNM had a significantly higher occurrence of TCI, multifocality and iNG (P=0.010, P=0.013 and P<0.001, respectively), and displayed significantly larger tumors than those with negative LLNM (1.56±1.18 cm vs. 0.96±0.61 cm; P<0.001). Furthermore, AYA patients with LLNM had significantly greater counts and larger positive CLN sizes than those without LLNM (both P<0.001; Table II).

Construction of risk prediction model of CLNM for patients within AYA group. Univariate and multivariate analyses were performed to identify independent risk factors for CLNM. Factors with P<0.05 underwent further multivariate analysis. A total of five factors were demonstrated to be independent risk factors for CLNM in the AYA patients: Male sex, TCI presence, multifocality, bilateral disease and MTD ≥1.0 cm (Table III). These factors contributed to the CLNM prediction model (Fig. 1A). The accuracy of the model was verified with 1,000 bootstrap resamples, yielding a C-index of 0.813 (95% CI, 0.774-0.853) and 0.804 after bootstrapping. The ROC curve and calibration plot are presented in Fig. 1B and C, indicating consistent actual and predicted CLNM probabilities.

Using the developed nomogram, each AYA patient received a CLNM risk score by summing the scores of the five factors. Patients were divided into two risk subgroups based on their scores, demonstrating significantly different central neck involvement rates (P<0.001; Table IV): i) Low CLNM risk [total score (TS) <50): CLNM rate of 25.9% (42/162) and ii) high CLNM risk (TS ≥50): CLNM rate of 81.1% (244/301).

Construction of risk prediction model of LLNM for AYA patients with positive CLNM. Multivariate analysis identified MTD ≥1.0 cm, maximum diameter of positive CLN ≥1.0 cm and iNG presence as independent LLNM risk factors for AYA patients with CLNM (Table III). A prediction model for LLNM was established using these three factors (Fig. 2A). The C-index values were 0.895 (95% CI, 0.854-0.936) and 0.886 post-bootstrapping. The accuracy of the model is shown in the ROC curve and calibration plot (Fig. 2B and C).

Table I. Clinicopathological characteristics of patients with papillary thyroid carcinoma within different groups.

A, All PTC patients that underwent thyroidectomy (n=952)

Characteristic	All patients (n=952)	AYA and old adult groups			Patients within AYA group		
		AYA group (n=463)	Older adult group (n=489)	P-value	15-29 years (n=156)	30-39 years (n=307)	P-value
Sex				0.045			0.081
Male	338 (35.5)	177 (38.2)	161 (32.9)		51 (32.7)	126 (41.0)	
Female	614 (64.5)	286 (61.8)	328 (67.1)		105 (67.3)	181 (59.0)	
Maximum tumor diameter, cm	0.92±0.66	0.98±0.80	0.80±0.63	<0.001	1.09±0.96	0.92±0.69	0.025
PTC with Hashimoto thyroiditis				0.028			0.357
No	757 (79.5)	356 (76.9)	401 (82.0)		116 (74.4)	240 (78.2)	
Yes	195 (20.5)	107 (23.1)	88 (18.0)		40 (25.6)	67 (21.8)	
PTC with nodular goiter				0.006			0.582
No	676 (71.0)	349 (75.4)	327 (66.8)		120 (76.9)	229 (74.6)	
Yes	276 (29.0)	114 (24.6)	162 (33.2)		36 (23.1)	78 (25.4)	
Thyroid capsular invasion				0.001			0.075
Absent	591 (62.1)	264 (57.0)	327 (66.9)		80 (51.3)	184 (59.9)	
Present	361 (37.9)	199 (43.0)	162 (33.1)		76 (48.7)	123 (40.1)	
Bilateral disease				0.474			0.249
Absent	773 (81.2)	372 (80.3)	401 (82.0)		130 (83.3)	242 (78.8)	
Present	179 (18.8)	91 (19.7)	88 (18.0)		26 (16.7)	65 (21.2)	
Multifocality				0.849			0.414
Absent	657 (69.0)	318 (68.7)	339 (69.3)		111 (71.2)	207 (67.4)	
Present	295 (31.0)	145 (31.3)	150 (30.7)		45 (28.8)	100 (32.6)	
Tumor location				0.543			0.399
Upper portion	270 (28.4)	121 (26.1)	149 (30.5)		37 (23.7)	84 (27.4)	
Middle/Lower portion	682 (71.6)	342 (73.9)	340 (69.5)		119 (76.3)	223 (72.6)	
CLNM				<0.001			0.179
No	495 (52.0)	177 (38.2)	318 (65.0)		53 (34.0)	124 (40.4)	
Yes	457 (48.0)	286 (61.8)	171 (35.0)		103 (66.0)	183 (59.6)	

B, Positive CLNM only (n=457)

Characteristic	All patients (n=952)	AYA and old adult groups			Patients within AYA group		
		AYA group (n=463)	Older adult group (n=489)	P-value	15-29 years (n=156)	30-39 years (n=307)	P-value
Number of positive CLN				<0.001			0.394
1-2	226 (49.5)	121 (42.3)	105 (61.4)		39 (37.9)	82 (44.8)	
3-4	118 (25.8)	74 (25.9)	44 (25.7)		31 (30.1)	43 (23.5)	
≥5	113 (24.7)	91 (31.8)	22 (12.9)		33 (32.0)	58 (31.7)	
Maximum diameter of positive CLN				0.034			0.573
<1.0 cm	349 (76.4)	211 (73.8)	138 (80.7)		78 (75.7)	133 (72.7)	
≥1.0 cm	108 (23.6)	75 (26.2)	33 (19.3)		25 (24.3)	50 (27.3)	

Table I. Continued.

Characteristic	All patients (n=952)	AYA and old adult groups			Patients within AYA group		
		AYA group (n=463)	Older adult group (n=489)	P-value	15-29 years (n=156)	30-39 years (n=307)	P-value
LLNM				0.009			0.386
No	344 (75.3)	205 (71.7)	139 (81.3)		77 (74.8)	128 (69.9)	
Yes	113 (24.7)	81 (28.3)	32 (18.7)		26 (25.2)	55 (30.1)	

Data are presented as n (%) or mean ± standard deviation. PTC, papillary thyroid carcinoma; AYA, adolescents and young adults; CLNM, central lymph node metastasis; CLN, central lymph node; LLNM, lateral lymph node metastasis.

Table II. Clinicopathological characteristics of adolescents and young adult patients.

Characteristic	AYA patients (n=463)			AYA patients with CLNM (n=286)		
	No-CLNM (n=177)	CLNM (n=286)	P-value	No-LLNM (n=205)	LLNM (n=81)	P-value
Sex			0.004			0.304
Male	53 (29.9)	124 (43.4)		85 (41.5)	39 (48.1)	
Female	124 (70.1)	162 (56.6)		120 (58.5)	42 (51.9)	
Thyroid capsular invasion			<0.001			0.010
Absent	149 (84.2)	115 (40.2)		92 (44.9)	23 (28.4)	
Present	28 (15.8)	171 (59.8)		113 (55.1)	58 (71.6)	
Bilateral disease			<0.001			0.090
Absent	158 (89.3)	214 (74.8)		159 (77.6)	55 (67.9)	
Present	19 (10.7)	72 (25.2)		46 (22.4)	26 (32.1)	
Maximum tumor diameter	0.73±0.61	1.13±0.86	<0.001	0.96±0.61	1.56±1.18	<0.001
Multifocality			<0.001			0.013
Absent	151 (85.3)	167 (58.4)		129 (62.9)	38 (46.9)	
Present	26 (14.7)	119 (41.6)		76 (37.1)	43 (53.1)	
Tumor location			0.704			0.012
Upper portion	48 (27.1)	73 (25.5)		161 (78.5)	52 (64.2)	
Middle/Lower portion	129 (72.9)	213 (74.5)		44 (21.5)	29 (35.8)	
PTC with nodular goiter			0.033			<0.001
No	143 (80.8)	206 (72.0)		163 (79.5)	43 (53.1)	
Yes	34 (19.2)	80 (28.0)		42 (20.5)	38 (46.9)	
PTC with Hashimoto thyroiditis			0.353			0.257
No	132 (74.6)	224 (78.3)		157 (76.6)	67 (82.7)	
Yes	45 (25.4)	62 (21.7)		48 (23.4)	14 (17.3)	
Number of positive CLN			-			<0.001
1-2	-	121 (42.3)		99 (48.3)	22 (27.2)	
3-4	-	74 (25.9)		60 (29.3)	14 (17.3)	
≥5	-	91 (31.8)		46 (22.4)	45 (55.6)	
Maximum diameter of positive CLN			-			<0.001
<1.0 cm	-	211 (73.8)		188 (91.7)	23 (28.4)	
≥1.0 cm	-	75 (26.2)		17 (8.3)	58 (71.6)	

Data are presented as n (%) or mean ± standard deviation. AYA, adolescents and young adults; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; CLN, central lymph node.

Table III. Univariate and multivariate analyses of cervical lymph node metastasis and lateral lymph node metastasis for AYA patients.

A, Analyzing all AYA patients to screen independent factors for CLNM

	Univariate analysis		Multivariate analysis	
Factor selected	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Sex (Male vs. female)	1.791 (1.203-2.665)	0.004	1.856 (1.144-3.010)	0.012
Thyroid capsular invasion (yes vs. no)	7.913 (4.956-12.633)	<0.001	7.262 (4.389-12.016)	<0.001
Bilateral disease (Yes vs. no)	2.798 (1.621-4.829)	<0.001	1.885 (1.002-3.546)	0.049
Maximum tumor diameter (≥1.0 cm vs. <1.0 cm)	2.728 (1.759-4.232)	<0.001	1.956 (1.169-3.274)	0.011
Tumor location (Upper vs. middle/lower)	0.921 (0.602-1.409)	0.704		
Multifocality (Yes vs. no)	4.138 (2.566-6.675)	<0.001	3.662 (2.110-6.356)	<0.001
PTC with nodular goiter (Yes vs. no)	1.633 (1.037-2.573)	0.034	1.137 (0.658-1.966)	0.646
PTC with Hashimoto thyroiditis (Yes vs. no)	0.812 (0.523-1.261)	0.353		

B, Analyzing AYA patients with positive CLNM to screen out independent factors for LLNM

	Univariate analysis		Multivariate analysis	
Factor selected	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Sex (Male vs. female)	1.311 (0.782-2.198)	0.305		
Thyroid capsular invasion (Yes vs. no)	2.053 (1.178-3.580)	0.011	2.129 (0.948-4.784)	0.067
Bilateral disease (Yes vs. no)	1.634 (0.924-2.890)	0.092		
Maximum tumor diameter (≥ 1.0 vs. <1.0 cm)	3.225 (1.892-5.496)	<0.001	2.740 (1.276-5.885)	0.010
Tumor location (Upper vs. middle/lower)	2.041 (1.162-3.585)	0.013	1.417 (0.632-3.181)	0.398
Multifocality (Yes vs. no)	1.921 (1.142-3.232)	0.014	1.809 (0.852-3.843)	0.123
PTC with nodular goiter (Yes vs. no)	3.430 (1.973-5.960)	<0.001	2.851 (1.306-6.225)	0.009
PTC with Hashimoto thyroiditis (Yes vs. no)	0.683 (0.353-1.323)	0.259		
Maximum diameter of positive CLN (≥1.0 vs. <1.0 cm)	27.887 (13.952-55.743)	<0.001	27.131 (12.372-59.496)	<0.001
Number of positive CLN (≥3 vs. <3)	2.505 (1.429-4.389)	0.001	1.618 (0.746-3.510)	0.223

PTC, papillary thyroid carcinoma; AYAs, adolescents and young adults; CLNM, central lymph node metastasis; CLN, central lymph nodes; LLNM, lateral lymph node metastasis.

Based on the LLNM prediction model, AYA patients with CLNM were categorized into three subgroups with varying LLNM rates (P<0.001, Table V): i) Low LLNM risk (TS=0): LLNM rate of 1.9% (2/106); ii) moderate LLNM risk (0<TS<100): LLNM rate of 20.0% (21/105); and iii) high LLNM risk (TS≥100): LLNM rate of 77.3% (58/75).

Cervical involvement risk assessment flow chart for AYA patients. The nomograms assessing CLNM and LLNM risk for AYA patients were combined into a comprehensive cervical risk evaluation chart (Fig. 3). In brief, for high-risk patients, options such as prophylactic CLND or more intensive postoperative monitoring may be considered. In the case of intermediate-risk patients, the choice between closer follow-up and prophylactic CLND should be made after thorough discussion with the patient, taking their preferences into account. For low-risk patients, a conservative 'wait and see' approach is advocated, negating the need for interventions like prophylactic cervical cleansing. In cases where no lymph node metastasis is detected through preoperative imaging, postoperative pathology (including lymph node specimens from prophylactic CLND) or in the 6-month postoperative follow-up imaging, the absence of lymph node metastasis is inferred at the initial diagnosis. These patients without lymph node metastasis would fall under low LLNM risk (total score=0) and would thus follow the recommendation for low-risk patients.

Other blood indexes. There were four thyroid-related hormone levels between AYA females and males that demonstrated significant variations. Triiodothyronine (T3) (1.58±0.22 nmol/l vs. 1.71±0.19 nmol/l; P<0.001), Thyroxine (T4) (96.42±16.89 nmol/l vs. 100.74±16.34 nmol/l; P=0.020), free T3 (FT3) (4.27±0.48 pmol/l vs. 4.55±0.44 pmol/l; P<0.001) and Thyroglobulin Antibody (TgAb) (106.23±227.03 kU/L vs. 49.85±186.09 kU/L; P=0.008) (Table SI).

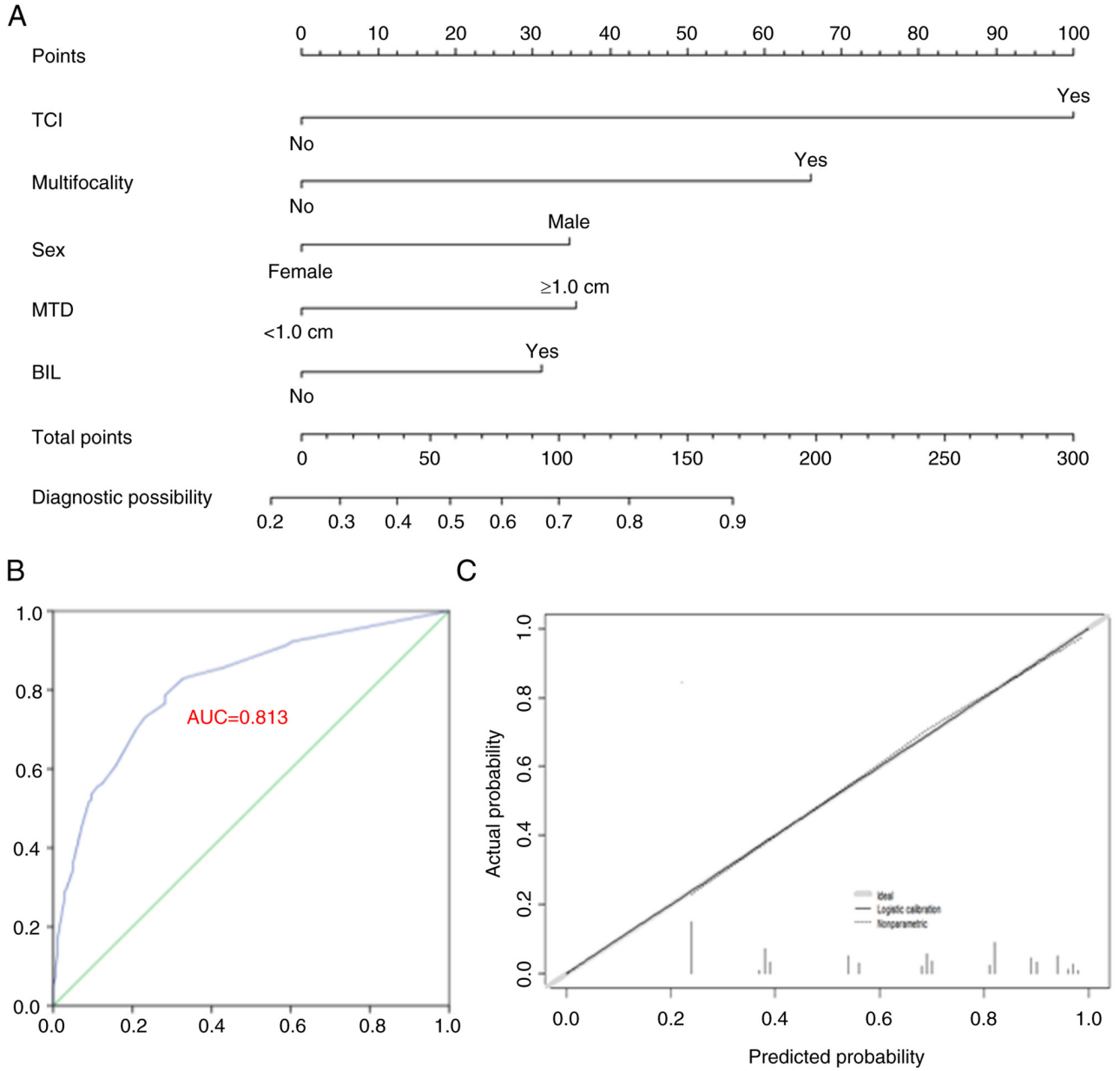

Figure 1. CLNM prediction model for AYA patients. (A) Nomogram illustrating CLNM risk for AYA patients. (B) Receiver operating characteristics curve and AUC representing the accuracy of the nomogram in predicting CLNM risk for this group. (C) Calibration curve for the prediction of the nomogram. CLNM, central lymph node metastasis; AYA, adolescents and young adults; AUC, area under the curve; TCI, thyroid capsular invasion; MTD, maximum tumor diameter; BIL, bilateral disease.

Discussion

The present study demonstrated that PTC tumors in patients aged 15-39 years (AYAs) were more aggressive, with AYA primary tumor sites differing significantly from older patients: They had larger tumors, more frequent TCI, ipsilateral Hashimoto thyroiditis and iNG. This suggests a faster and more complex disease progression in AYAs. Moreover, lymph node involvement in both central and lateral regions was higher in AYAs. They also had more extensive CLNM, indicating greater local tumor invasiveness. Within the AYA group, primary tumor and lymph node conditions were consistent across ages 15-29 and 30-39 years.

Use of more aggressive treatments such as prophylactic CLND for PTC is debated (12). An active surveillance approach instead of traditional surgery has been gaining traction lately for certain PTC types, but comprehensive factors to be considered for different approaches remain unclear. Age, a vital factor to consider in PTC clinical staging as per the 8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging (13), may serve as a viable starting point. Although select few research, such as those by Vriens *et al* (11) and Miccoli *et al* (14), reported AYAs to have lower staging and improved prognoses, more studies reported advanced PTC with neck involvement in this demographic (15), which align with the findings of the current study. Managing the cervical lymph node region is thus crucial for AYAs, and this should be based on investigations into lymph node metastasis risk to account for the larger tumor size and more frequent multifocality seen in AYA patients with PTC (10,14).

Table IV. Risk stratification of CLNM for adolescents and young adult patients.

CLNM	Low risk (TS <50; n=162)	High risk (TS ≥50; n=301)	P-value
Negative	120 (74.1)	57 (18.9)	<0.001
Positive	42 (25.9)	244 (81.1)	

CLNM, central lymph node metastasis; TS, total score.

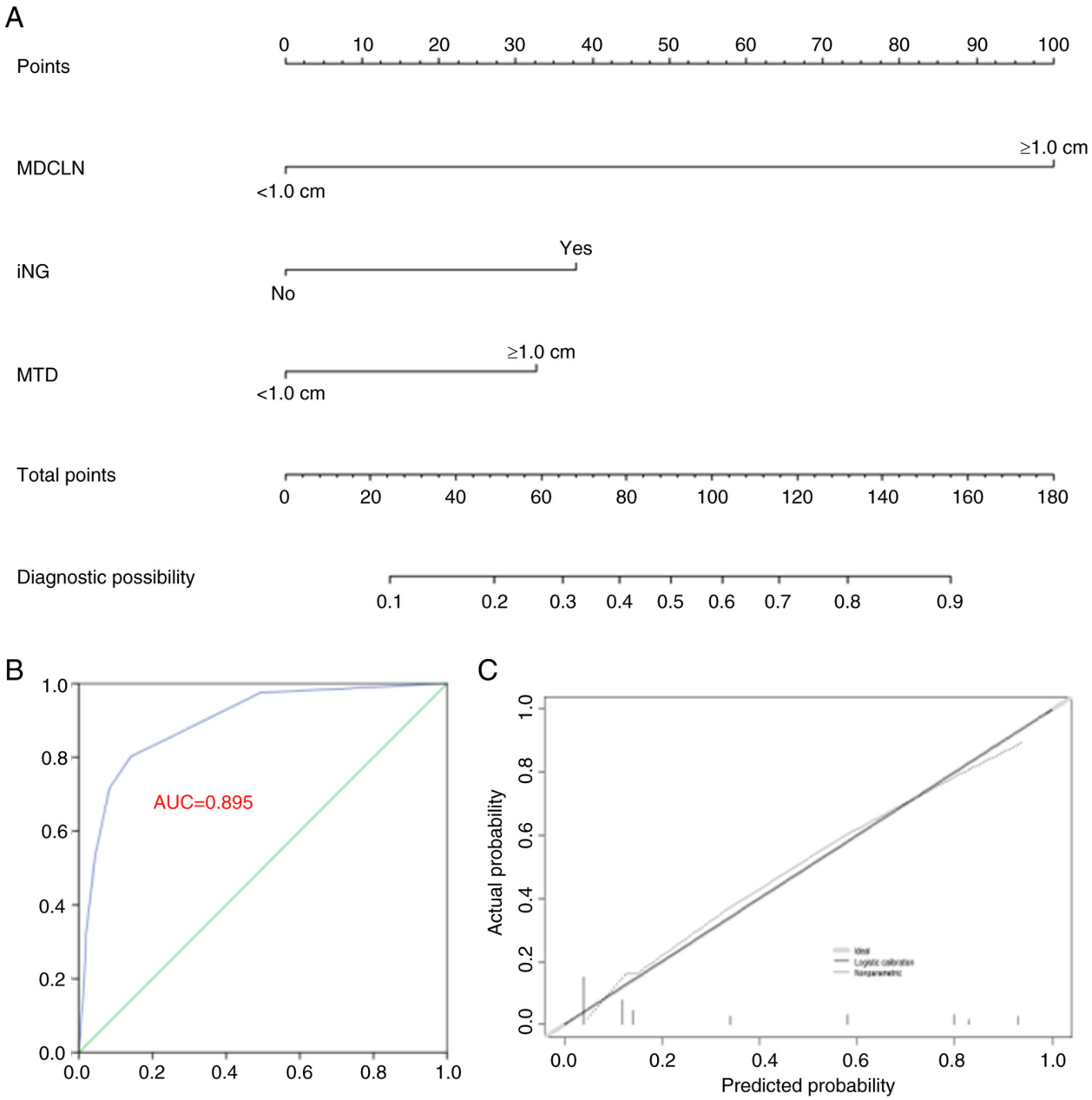

Figure 2. LLNM prediction model for AYA patients with positive CLNM. (A) Nomogram showcasing LLNM risk in AYA patients with positive CLNM. (B) Receiver operating characteristics curve and AUC demonstrates the accuracy of the nomogram in predicting LLNM risk for this group. (C) Calibration curve demonstrating the prediction of the nomogram, comparing actual likelihood to predicted likelihood. LLNM, lateral lymph node metastasis; CLNM, central lymph node metastasis; AUC, area under the curve; MDCLN, maximum diameter of positive central lymph nodes; iNG, ipsilateral nodular goiter; MTD, maximum tumor diameter.

For AYA patients, of the five key risk factors for CLNM, four (MTD ≥1.0 cm, presence of TCI, multifocality and bilateral disease) are seen as indicators of advanced tumor progression and are often linked with CLNM in patients with PTC, as reported in several studies (9,16,17). Male AYAs are at high risk for central neck metastasis, a factor not previously

Table V. Risk stratification of LLNM for adolescents and young adult patients with positive central LNM.

LLNM	Low risk (TS=0; n=106)	Moderate risk (0< TS <100; n=105)	High risk (TS ≥100; n=75)	P-value
Negative	104 (98.1)	84 (80.0)	17 (22.7)	<0.001
Positive	2 (1.9)	21 (20.0)	58 (77.3)	

LLNM, lateral lymph node metastasis; TS, total score.

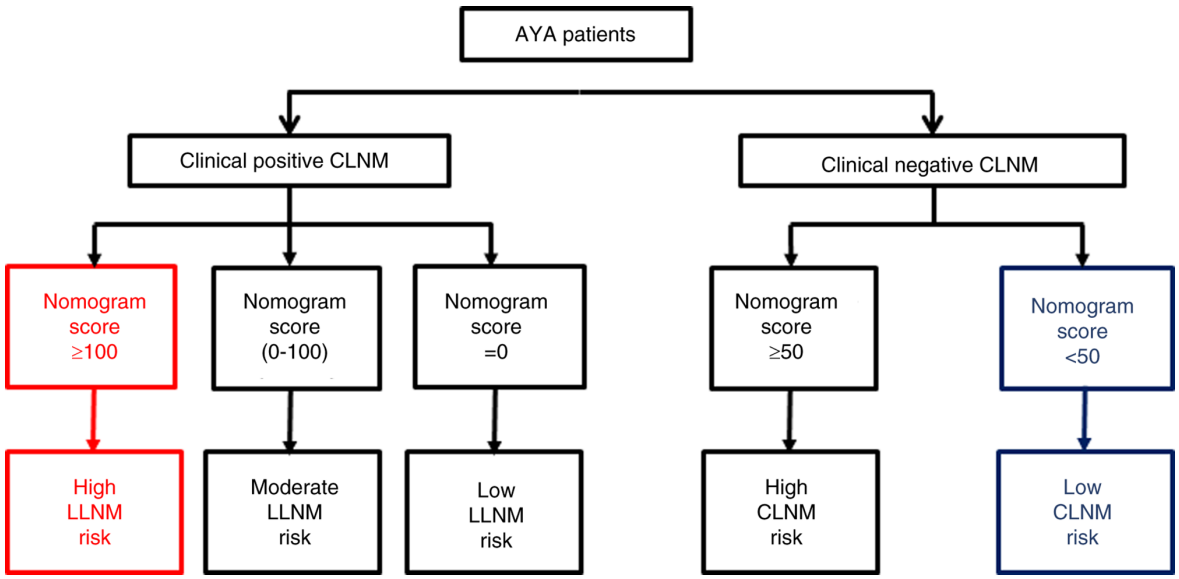

Figure 3. Flow chart depicting the risk of CLNM for AYA patients with papillary thyroid carcinoma, covering both CLNM and LLNM. AYA, adolescents and young adults; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis.

associated with patients with PTC (18), hence more studies are needed to support this finding. At this stage, we hypothesize that such a discrepancy between the sexes may relate to differing thyroid hormone levels. The analysis of blood indexes in AYA males and females in the present study (Table SI) demonstrated significant variations in T3, T4, FT3 and TgAb levels, hinting at new research avenues on CLNM risk.

The present study also identified high-risk factors for LLNM in AYA patients with positive CLNM. A total of three main factors were recognized, including two related to primary tumors (MTD ≥1.0 cm and presence of iNG) and one associated with central neck regions (maximum diameter of positive CLN ≥1.0 cm). Based on these risks, two prediction models were developed for assessing CLNM and LLNM risks in AYA patients. Based on the distribution of the total score described in the newly-created nomogram for predicting CLNM risk, AYA patients were split into two groups. The overall CLNM rate was 61.8% (286/463). The low-risk group had a CLNM rate of 25.9% (42/162) and the rate of the high-risk group was 81.1% (244/301). Furthermore, AYA patients with positive CLNM were categorized into three groups with LLNM rates of 1.9, 20.0 and 77.3%. This classification is supported by previous studies (19,20), demonstrating its effectiveness in screening patients with extremely low LLNM risk (only 2/106 patients in this subgroup showed positive lateral neck involvement).

Two prediction models were merged to form a CLNM risk assessment for AYA patients. For AYA patients without clinical signs of CLNM, preventive central neck dissection should be considered for those at high CLNM risk; however, for patients with low CLNM risk, the decision should be based on the surgeon's assessment and patient preference. If no surgery is performed, closer monitoring is advised. For AYA patients with detected positive CLNM, no preventive measures are necessary for those at low LLNM risk; however, patients with high LLNM risk may require close observation and possibly preventive lateral neck dissection.

The present study has certain limitations. Firstly, the patient sample was obtained from one center with a limited case count. For stronger evidence, a larger, multicenter sample is required. The research was also retrospective, so the predictive model needs validation in a prospective trial. Furthermore, only lymph node metastasis for subgroup endpoints was assessed. Future research should have a broader postoperative follow-up to understand the long-term outcomes for these subgroups. Genetic testing was also not performed and therefore, the role of several mutations, such as Braf-V600E and TERT were not assessed in the current study. Moreover, due to the short median follow-up time, it was not possible to provide significant disease-free survival and overall survival rates for patients with PTC.

In conclusion, patients with PTC aged 15-39 years were more at risk for larger tumor sizes, ipsilateral Hashimoto thyroiditis, thyroid capsular invasion, CLNM, LLNM and larger CLN sizes and counts. Therefore, a stratification chart was developed for AYA patients with PTC to quantify the risk of both CLNM and LLNM, assisting with the clinical decisions for these patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LW and GC conceived and designed the study and analyzed and interpreted data. YY conceived and designed the study. LW and YY wrote the manuscript. JL, ZJ and YZ collected, analyzed and interpreted data. LW and GC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The authors take responsibility for the accuracy and integrity of the present work, addressing any related concerns. The study adhered to the Declaration of Helsinki and was approved by the ethics committee of Ningbo Medical Center Lihuili Hospital (Ningbo, China; approval no. KY2022SL341-01). Informed consent for the present retrospective review was waived by the same committee. The present study is registered at the Chinese Clinical Trials Registry (trial registration no. ChiCTR2200064921).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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