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The prognostic value of lymph node metastasis and the eighth edition of AJCC for patients with anaplastic thyroid cancer

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Abstract

Objective: The eighth edition of the American Joint Committee on Cancer (AJCC-v8) for anaplastic thyroid cancer (ATC) made a revision in staging for patients with lymph node metastasis (LNM) based on the seventh edition of AJCC (AJCC-v7). Our study aimed to evaluate the predictive ability of AJCC-v8 for survival in patients with ATC by exploring the association between lymph node stage and prognosis of ATC patients.

Methods: Retrospective study of ATC in Surveillance, Epidemiology and End Results (SEER) database. The association between LNM and survival of ATC was estimated by the Kaplan-Meier method and Cox regression model. The predictive performances of the AJCC-v8 and AJCC-v7 were estimated through C-index, Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Results: A total of 313 patients with ATC were included in our analysis. Notably, LNM was identified as an independent risk factor for ATC mortality (adjusted HR, 1.47, 95% CI, 1.10–1.96; p = .009), while the risk of mortality in N1a group was comparable to that in N1b group according to univariate (HR, 1.30, 95% CI, 0.92–1.82; p = .133) and multivariate (adjusted HR 0.87, 95% CI, 0.60–1.27; p = .467) cox analyses. Applying the AJCC-v8, the survival of migration population staged T1-3aN1M0 was significantly worse than that of T1-3aN0M0 patients (IVA stage), while was not different from that of T3b-T4bN0/N1M0 patients (IVB stage). With a higher C-index (0.60 vs. 0.59), lower AIC (2728 vs. 2732) and BIC (2732 vs. 2735), AJCC-v8 was demonstrably a more favourable prediction model than AJCC-v7.

Conclusions: This study demonstrated that LNM was independently associated with poor prognosis of ATC, and AJCC-v8 with the modified staging of patients with LNM showed better survival predictive performance in ATC patients than AJCC-v7.

KEYWORDS
AJCC, anaplastic thyroid cancer, lymph node metastasis, Survival

Hanpu Zhang and Yan-Ci Zhao are contributed equally to this work.

1 | INTRODUCTION

In recent decades, thyroid cancer has garnered increasing attention due to its high incidence and people's growing demand for health.[1,2] Thyroid cancer is classified into four pathological patterns, which are papillary, follicular, medullary and anaplastic thyroid cancer (ATC).[3] Notably, ATC is completely different from the other three types of thyroid cancer, which have favourable prognosis. In contrast, ATC is the least common type and extremely aggressive and lethal, disproportionately accounting for between 20% and 50% of all deaths from thyroid cancer.[4] The median overall survival (OS) is only 3.16 months according to a recent Surveillance, Epidemiology, and End Results (SEER) database analysis.[5] As ATC is very rare, representing only 1%~2% of all thyroid cancers,[6] there has not been enough research on its diagnosis, treatment or prognostic evaluation to date.

The American Joint Committee on Cancer (AJCC) staging manual is a universal tool for the prognostic evaluation of patients with thyroid cancer. The eighth edition of the AJCC (AJCC-v8) staging system, revised on the basis of the seventh edition of the AJCC (AJCC-v7), was published in 2016 and was officially implemented on 1 January 2018.[7] For consistency, the AJCC-v8 designates all ATC as stage IV (IVA, IVB and IVC) thyroid cancer based on the tumour, lymph node and metastasis (TNM) concept, which is the same as that presented in the AJCC-v7. Notably, the AJCC-v7 staging system was based on whether a tumour has extrathyroidal extension and distant metastasis,[8] while the AJCC-v8 presents a revision to the AJCC-v7 by adding lymph node status as a staging element.[7] However, current evidences on the association between lymph node status and survival of ATC remain limited and have failed to figure out the association between LNM and prognosis of ATC.[9–11] Therefore, the prognostic predictive value of LNM still needs to be verified, and the survival predictive ability of AJCC-v8 staging system with lymph node status served as the grading standard also needs to be evaluated urgently.

Notably, based on the distribution of neck lymph node clusters, the location of lymph node metastasis is divided into seven regions (I-VII). Level VI and level VII (upper mediastinal) lymph nodes are classified as central neck lymph nodes (N1a), whereas level I-V lymph nodes belong to lateral ones (N1b) in AJCC-v8.[7] Recent researches on differentiated thyroid cancer indicated that survival was worse for patients in stage N1b than for patients in stage N1a,[12–16] and there is growing concern that the mortality risk for N1b patients could be underestimated in the AJCC-v8.[14–16] However, the impact of the N1a and N1b stages on survival for patients with ATC remains unknown.

Therefore, in the current study, we conducted a retrospective research based on SEER database to thoroughly investigate the association of lymph node status with the survival of ATC and to evaluate the performance of the AJCC-v8 staging system in detail.

2 | MATERIALS AND METHODS

2.1 | Study population and experimental process

Data were extracted from the SEER database (SEER-18) registries, which were submitted by the National Cancer Institute in November 2018. Patients with ATC were identified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 8020-8035 and topography code C73.[4] SEER*Stat version 8.3.8 was used to generate a case list file. Obtaining data from the SEER database does not require a patient consent form, as all the data were de-identified before publishing and contain no personally identifiable information.

Information about patient demographics (age and sex), tumour characteristics (tumour size, extrathyroidal extension, multifocality, lymph node status, distant metastasis and AJCC-v7 stage), treatment (surgery, radiotherapy and chemotherapy), survival status and survival time for each case was selected from medical records. Specifically, the information of lymph node status was obtained from the record in variable 'Derived AJCC N, 7th ed (2010–2015)' of SEER database, which was diagnosed based on the pathologic sources including resection, biopsy or aspiration of regional lymph nodes. The stages of N1a, N1b and N1NOS were defined as LNM, and N0 stage was defined as the absence of LNM. In particular, patients with NX stage indicating that region lymph nodes could not be evaluated were ruled out. The classification of N1a and N1b in

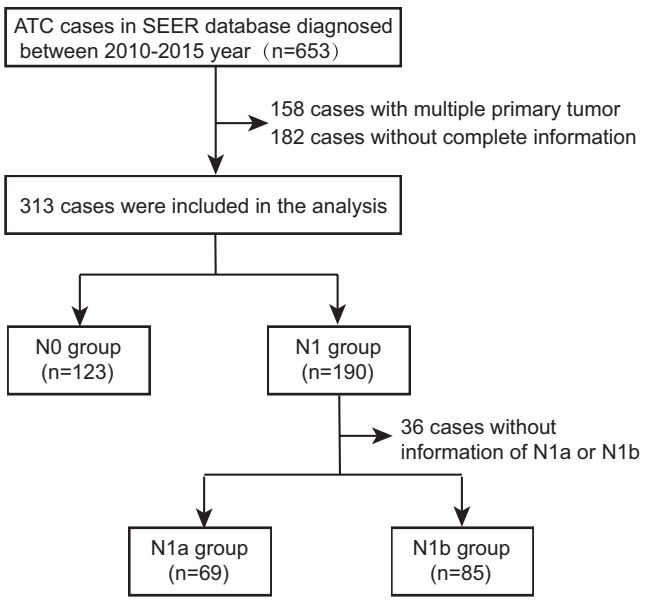

FIGURE 1 The flow chart of participant enrolment. The data from 313 patients diagnosed with primary ATC between 2010 and 2015 with fully recorded information were included in the study. According to the presence of LNM, patients were divided into N1 group (*N* = 190) and N0 group (*N* = 123). Among the N1 group, 154 cases with definite regional LNM were further divided into the N1a and N1b groups based on the AJCC-v8

AJCC-v8 was based on information about regions of LNM from the variable 'CS lymph nodes (2004–2015)' in SEER database. The information of distant metastasis was obtained from 'Derived AJCC M, 7th ed (2010–2015)' in SEER database. According to the definition and classification of AJCC-v8 (Table S1 and Table S2), we defined the AJCC-v8 stage of ATC patients based on the SEER data of tumour extension, lymph node status and distant metastasis. Furthermore, according to the scope of thyroidectomy and the number of lymph nodes removed recorded in variables 'RX Summ-Scope Reg LN Sur (2003+)' and 'RX Summ-Surg Prim Site (1988+)' of SEER, we divided the operation methods into four types: no surgery, thyroidectomy without lymph node dissection, thyroidectomy with lymph node dissection (1–3) and thyroidectomy with lymph node dissection (4 and more). Due to the fact that age and tumour size in the SEER database were recorded as a range rather than a specific number in some cases, we converted the continuous variables such as age and tumour size into categorical variables. Specifically, patients were divided into groups of people <70 and ≥70 years old, since an age ≥70 years has been identified as a risk factor for ATC prognosis in previous studies.[9,11] Tumour size was divided into four categories (≤4 cm, 4.1–6 cm, 6.1–8 cm and >8 cm).[17]

Considering that the AJCC-v7 has been in use since 2009 and the information on AJCC-v7 stage is provided in the SEER database only for records from 2010 to 2015, we enrolled 653 patients with ATC diagnosed between 2010 and 2015. The specific exclusion criteria were as follows: (1) 158 cases having multiple primary tumours or (2) 182 cases without complete information on the aforementioned variables. Finally, 313 cases were included, and cases were divided into N1 group (*N* = 190) and N0 group (*N* = 123) according to the diagnosis of LNM. As 36 cases with code 170 [I-V and VII regional lymph nodes] and codes 180, 500 and 800 [unknown regional lymph node] in variable 'CS lymph nodes (2004–2015)' of SEER database lacked essential information for the definition of N1a and N1b in AJCC-v8, only 154 patients with LNM were further divided into N1a group (*N* = 69) and N1b group (*N* = 85). A general description of participant enrolment is presented in Figure 1.

2.2 | Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 25) and R software (R Foundation; version 3.6.3). Descriptive statistics were used to analyse the characteristics of patient groups stratified by lymph node status. Differences in categorical variables were compared using chi-square tests or Fisher's exact test. Univariate and multivariate Cox regression analyses were used to determine the association between lymph node status and survival of patients with ATC. Furthermore, we also conducted a subgroup analysis of the relationship between LNM and survival of ATC based on the stratification according to clinicopathological factors that significantly related to survival. The subgroup analysis was displayed in a forest plot that was generated by forestplot package in R. OS and cancer-specific survival (CSS) by the lymph node status and stages identified in the AJCC-v7 and AJCC-v8 were determined by the Kaplan–Meier (K–M) method and were compared by log-rank test with SPSS. To compare the statistical model performances based on the two editions, the concordance index (Harrell's C-index),[18] Akaike information criterion (AIC)[19] and Bayesian information criterion (BIC)[20] of survival were calculated by the survival package in R.[21] The C-index measures the discrimination between predicted probability and actual outcome. The AIC and BIC measure the goodness of statistical model fit and are commonly used to estimate the relative quality of a statistical model. A model with high C-index and low AIC and BIC scores is considered to be better for predicting outcomes. Notably, a two-sided *p* value of .05 was considered statistically significant for all analyses.

3 | RESULTS

3.1 | Population characteristics

A total of 313 patients diagnosed with ATC in the 2010–2015 period were included in the analysis. With a median follow-up period of 3 months (range, 0–82 months), there were 277 (88.5%) deaths, including 265 (84.7%) deaths from ATC. In the study population, 190 (60.7%) patients with ATC presented with LNM (N1 group). Patients with LNM were older and had a higher incidence of extrathyroidal extension (85.8% vs. 74.0%) and distant metastasis (56.3% vs. 26.8%) than those without LMN (N0 group) (Table 1). With regard to treatment, we found that only 32.6% of ATC patients received surgery, and the rates of radiotherapy and chemotherapy were 59.4% and 48.9%, respectively. Compared with N0 group, a higher incidence of surgery was observed in patients with LNM (36.8% vs. 26.0%). Thyroidectomy with lymph node dissection (4 or more) was the most common surgical approach among patients staged N1 with a rate of 22.6%, while thyroidectomy with lymph node dissection (from 1 to 3) was the most common treatment for patients staged N0 with a rate of 16.3% (Table 1). There was no significant difference in the frequency of radiotherapy or chemotherapy between patients with LNM and those without.

3.2 | LNM was independently associated with poor survival of ATC

Although the lymph node status has been added to the AJCC-v8 staging system as a grading standard, there is still a lack of evidence to support the association between LNM and survival of ATC. Therefore, we undertook experiments to determine whether LNM is a risk factor for the mortality of patients with ATC through K-M method and Cox regression analysis. The survival curves indicated that patients with LNM had significantly worse OS (*p* = .018) and CSS (*p* = .018) than those without LNM (Figure 2). Meanwhile, the risk of death in the N1 group increased by about 1.3-fold according

TABLE 1 Clinicopathological characteristics of ATC patients

	Total (*n* = 313)	N0 (*n* = 123)	N1 (*n* = 190)	*p* Value
Age (years)				
<70	174 (55.6%)	57 (46.3%)	117 (61.6%)	.008
≥70	139 (44.4%)	66 (53.7%)	73 (38.4%)	
Sex				
Female	175 (55.9%)	73 (59.3%)	102 (53.7%)	.324
Male	138 (44.1%)	50 (40.7%)	88 (46.3%)	
Tumour size (cm)				
≤4	49 (15.7%)	21 (17.1%)	28 (14.7%)	.070
4.1–6	85 (27.2%)	41 (33.3%)	44 (23.2%)	
6.1–8	104 (33.2%)	31 (25.2%)	73 (38.4%)	
>8	75 (24.0%)	30 (24.4%)	45 (23.7%)	
Extrathyroidal extension				
Localized	59 (18.8%)	32 (26.0%)	27 (14.2%)	.019
Minor extension*	12 (3.8%)	2 (1.6%)	10 (5.3%)	
Major neck structures	119 (38.0%)	48 (39.0%)	71 (37.4%)	
Blood vessels or prevertebral fascia	123 (39.3%)	41 (33.3%)	82 (43.2%)	
Multifocality				
No	248 (79.2%)	100 (81.3%)	148 (77.9%)	.468
Yes	65 (20.8%)	23 (18.7%)	42 (22.1%)	
Distant metastasis				
No	173 (55.3%)	90 (73.2%)	83 (43.7%)	<.001
Yes	140 (44.7%)	33 (26.8%)	107 (56.3%)	
Surgery				
No surgery	211 (67.4%)	91 (74.0%)	120 (63.2%)	.003
Thyroidectomy without lymph node dissection	8 (2.6%)	3 (2.4%)	5 (2.6%)	
Thyroidectomy with lymph node dissection (1–3)	42 (13.4%)	20 (16.3%)	22 (11.6%)	
Thyroidectomy with lymph node dissection (4 and more)	52 (16.6%)	9 (7.3%)	43 (22.6%)	
Radiotherapy				
No	127 (40.6%)	53 (43.1%)	74 (38.9%)	.466
Yes	186 (59.4%)	70 (56.9%)	116 (61.1%)	
Chemotherapy				
No	160 (51.1%)	71 (57.7%)	89 (46.8%)	.060
Yes	153 (48.9%)	52 (42.3%)	101 (53.2%)	

*Minor extension, gross extrathyroid extension invading only strap muscles.

to univariate cox model (OS: hazard ratio [HR] 1.32, 95% confidence interval [CI], 1.03–1.68, $p = .028$; CSS: HR 1.33, 95% CI, 1.03–1.71, $p = .028$) (Table 2). Applying multivariate Cox proportional analysis with an adjustment of the clinicopathologic characteristics and therapies, we determined that LNM was still independently associated with increased risk of mortality in ATC (OS: adjusted HR, 1.47, 95% CI, 1.10–1.96; $p = .009$; CSS: adjusted HR, 1.44, 95% CI, 1.07–1.94; $p = .015$) (Figure 3). In addition, in the univariate and multivariate Cox models, tumour size, extrathyroidal extension and distant metastasis were consistently determined to be risk factors for poor OS and CSS for patients with ATC, while surgery, chemotherapy and radiotherapy all showed the ability to improve prognosis. Notably, there showed no significant difference in survival between ATC patients who had received thyroidectomy without lymph node dissection

TABLE 2 Univariate and multivariate Cox regression analyses for overall survival and cancer-specific survival of ATC

	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age (years)								
<70	Reference		Reference		Reference		Reference	
≥70	1.32 (1.04,1.67)	.021	1.30 (1.01,1.67)	.044	1.26 (0.99,1.60)	.064	1.24 (0.95,1.60)	.109
Sex								
Female	Reference		Reference		Reference		Reference	
Male	0.91 (0.72,1.16)	.459	1.08 (0.84,1.39)	.537	0.90 (0.71,1.15)	.405	1.06 (0.82,1.37)	.685
Tumour size (cm)								
≤4	Reference		Reference		Reference		Reference	
4.1–6	1.03 (0.70,1.51)	.900	1.41 (0.95,2.09)	.092	1.02 (0.69,1.52)	.910	1.40 (0.93,2.11)	.103
6.1–8	1.37 (0.95,1.99)	.094	1.50 (1.02,2.20)	.039	1.39 (0.95,2.03)	.093	1.50 (1.01,2.22)	.045
>8	2.08 (1.40,3.08)	<.001	2.38 (1.58,3.58)	<.001	2.13 (1.43,3.18)	<.001	2.44 (1.61,3.71)	<.001
Extrathyroidal extension								
Localized	Reference		Reference		Reference		Reference	
Minor extension*	1.20 (0.59,2.45)	.619	1.53 (0.72,3.26)	.270	1.28 (0.62,2.63)	.502	1.62 (0.76,3.47)	.214
Major neck structures	1.25 (0.88,1.76)	.216	1.44 (1.00,2.06)	.051	1.27 (0.89,1.81)	.193	1.46 (1.01,2.13)	.046
Blood vessels or prevertebral fascia	1.63 (1.16,2.29)	.005	1.53 (1.06,2.20)	.023	1.68 (1.18,2.39)	.004	1.56 (1.08,2.28)	.019
Multifocality								
No	Reference		Reference		Reference		Reference	
Yes	0.90 (0.67,1.21)	.497	1.01 (0.74,1.40)	.933	0.91 (0.67,1.23)	.526	1.01 (0.73,1.40)	.946
Lymph node metastasis								
No	Reference		Reference		Reference		Reference	
Yes	1.32 (1.03,1.68)	.028	1.47 (1.10,1.96)	.009	1.33 (1.03,1.71)	.028	1.44 (1.07,1.94)	.015
Distant metastasis								
No	Reference		Reference		Reference		Reference	
Yes	1.78 (1.40,2.26)	<.001	1.47 (1.12,1.92)	.005	1.86 (1.45,2.38)	<.001	1.53 (1.16,2.02)	.002
Surgery								
No surgery	Reference		Reference		Reference		Reference	
Thyroidectomy without lymph node dissection	0.81 (0.40,1.65)	.569	0.57 (0.26,1.23)	.150	0.84 (0.42,1.72)	.640	0.58 (0.27,1.26)	.169
Thyroidectomy with lymph node dissection (1–3)	0.52 (0.36,0.75)	<.001	0.63 (0.42,0.93)	.019	0.51 (0.35,0.75)	.001	0.63 (0.42,0.94)	.023
Thyroidectomy with lymph node dissection (4 and more)	0.52 (0.37,0.74)	<.001	0.45 (0.30,0.66)	<.001	0.53 (0.38,0.75)	<.001	0.45 (0.31,0.67)	<.001
Radiotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.43 (0.34,0.55)	<.001	0.49 (0.35,0.67)	<.001	0.42 (0.33,0.54)	<.001	0.47 (0.34,0.65)	<.001

(Continues)

TABLE 2 (Continued)

Variables	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.50 (0.39,0.64)	<.001	0.70 (0.51,0.96)	.025	0.50 (0.39,0.64)	<.001	0.70 (0.51,0.97)	.032

*Minor extension, gross extrathyroid extension invading only strap muscles

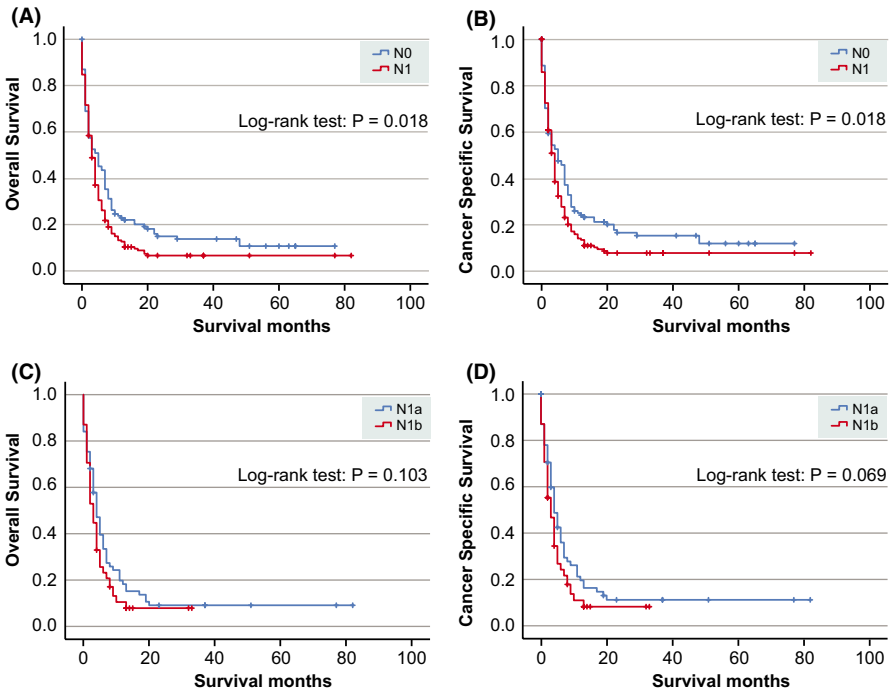

FIGURE 2 Survival curves for patients with ATC in N1 group versus N0 group and N1a group versus N1b group. (A and B) The curves for overall survival and cancer-specific survival of patients with stage N1 versus those with stage N0. (C and D) The curves for overall survival and cancer-specific survival of patients with stage N1a versus those with stage N1b. The *p* value was estimated by the log-rank test. The dots indicate censoring

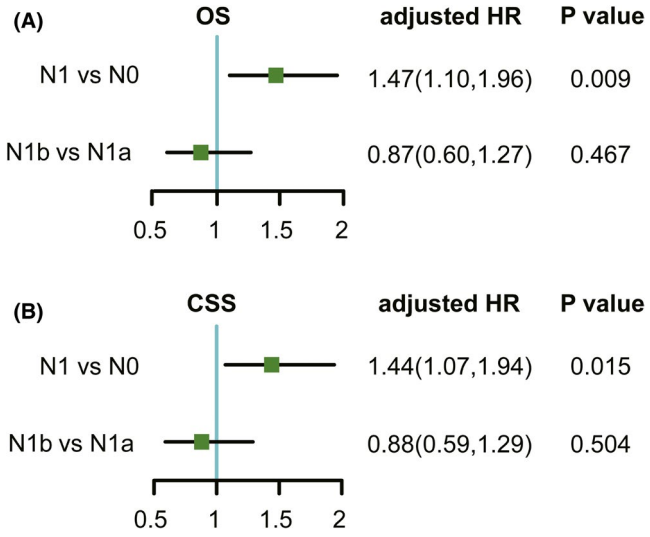

FIGURE 3 Hazard ratios for survival in N1 group versus N0 group and N1b group versus N1a group by multivariate cox model. Forest plot of the adjusted hazard ratios for overall survival (A) and cancer-specific survival (B) in N1 group versus N0 group and N1b versus N1a group

and those without surgery. Nevertheless, thyroidectomy with lymph node dissection (1–3) (OS: adjusted HR, 0.63, 95% CI, 0.42–0.93; p = .019) and thyroidectomy with lymph node dissection (4 and more) (OS: adjusted HR, 0.45, 95% CI, 0.30–0.66; p < .001) were both found to improve the survival of ATC (Table 2). Furthermore, we conducted a subgroup analysis of the association between LNM and survival of ATC. These subgroups were classified according to the aforementioned clinicopathological characteristics related to the prognosis of ATC. Interestingly, LNM was found to be associated with the prognosis of patients with ATC who were aged ≥70 or with a tumour size of 4.1–6 cm or a localized tumour (Figure S1).

3.3 | No Significant Difference in survival of ATC between N1a and N1b group

In this study, 154 patients among the N1 group were further classified as N1a group (cases with VI, VII regional LNM) and N1b group (cases with I-V regional LNM). The clinicopathologic features and treatment information of patients in N1a and N1b groups are summarized in the Table S3. Compared with N1a group,

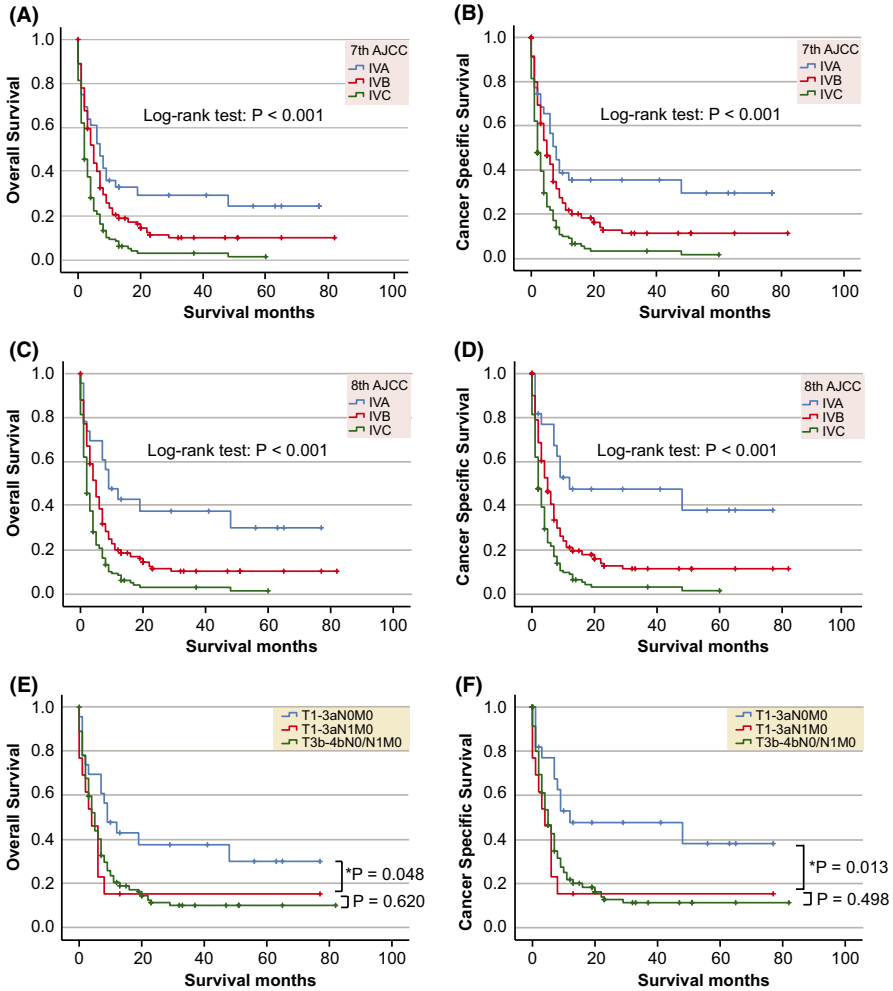

FIGURE 4 Survival curves of patients with ATC according to the seventh and eighth editions of AJCC staging system. (A and C) The overall survival curves of patients with different stages based on the seventh and eighth editions of the AJCC, respectively. (B and D) The cancer-specific survival curves of patients with different stages based on the seventh and eighth editions of the AJCC, respectively. (E and F) Comparison of the overall survival and cancer-specific survival curves of patients in stages T1-3aN0M0, T1-3aN1M0 and T3b-4bN0/N1M0, respectively. The P value was estimated by the log-rank test. The dots indicate censoring

the incidence of distant metastasis (63.5% vs. 47.8%) was higher in N1b group, while the proportion of patients undergoing surgery (30.6% vs. 50.7%) and radiotherapy (54.1% vs. 69.6%) was lower. As for the mortality, there were 61 deaths (88.4%) in the N1a group and 77 deaths (90.6%) in the N1b group. By the K–M method, it showed that there was no statistical difference in OS (log-rank test: p = .103) and CSS (log-rank test: p = .069) between the N1a group and the N1b group (Figure 2). Meanwhile, the risk of all-cause mortality appeared to be comparable between N1a and N1b groups according to univariate (HR, 1.30, 95% CI, 0.92–1.82; p = .133) and multivariate (adjusted HR, 0.87, 95% CI, 0.60–1.27; p = .467) cox analyses (Figure 3A). The CSS of N1b group also showed no significant difference from that of N1a group (univariate Cox: HR, 1.35, 95% CI, 0.95–1.91; p = .094; multivariate Cox: adjusted HR, 0.88, 95% CI, 0.59–1.29; p = .504) (Figure 3B).

3.4 | The eighth edition of AJCC with reclassification of patients with LNM showed better predictive performance for the prognosis of ATC patients

According to the definition of TNM and the classification systems of AJCC-v7 and AJCC-v8 (Table S1 and Table S2), the modified definition of T stage and N stage will not affect the classification[7,8,22]. In fact, the major change made in AJCC-v8 is that ATC confined to the thyroid gland has been reclassified into IVB stage based on the presence of LNM, which was classified as the IVA stage in the previous AJCC-v7. Considering the negative correlation between LNM and survival of patients with ATC, especially those with localized tumour (Figure S1), we speculate that upgrading the IVA stage patients with LNM to IVB stage could help improve the prognostic predictive performance of the grading system.

As shown in Figure S2, using the AJCC-v7, 36 (11.5%) patients were classified in stage IVA, 137 (43.8%) in stage IVB and 140 (44.7%) in stage IVC. Applying the eighth edition, 13 patients defined as T1-3aN1M0 were upgraded from the IVA stage to IVB stage, while the ratings of the others remained unchanged. Firstly, we analysed the OS and CSS across different AJCC stages by the K–M method. It was determined that OS and CSS were both significantly different among IVA, IVB and IVC stages classified by AJCC-v7 (Figure 4A,B) and AJCC-v8 (Figure 4C,D) (all with p < .001). Furthermore, there was greater separation between the OS and CSS curves for patients in stages IVA and IVB in the AJCC-v8 than in the AJCC-v7. Further comparisons of the OS and CSS of the migration population in stage T1-3aN1M0 (IVB stage in the AJCC-v8), T1-3aN0M0 (IVA stage in the AJCC-v8) and T3b-T4bN0/N1M0 (IVB stage in the AJCC-v8) are illustrated in Figure 4E,F, , respectively. The OS and

TABLE 3 The performance of AJCC-v7 and AJCC-v8 for prediction of OS and CSS in ATC patients

Ed.	Stage	Cox regression analysis for OS		Cox regression analysis for CSS		Model performance for OS prediction			Model performance for CSS prediction		
		HR (95% CI)	*p*Value	HR (95% CI)	*p* Value	C-index	AIC	BIC	C-index	AIC	BIC
AJCC-v7	IVA	Reference				0.59 (0.55, 0.63)	2732	2735	0.60 (0.56, 0.64)	2609	2612
	IVB	1.47 (0.96, 2.25)	.079	1.58 (1.00, 2.48)	.048						
	IVC	2.41 (1.57, 3.70)	<.001	2.68 (1.71, 4.20)	<.001						
AJCC-v8	IVA	Reference				0.60(0.56, 0.63)	2728	2732	0.61 (0.57, 0.65)	2604	2608
	IVB	1.93 (1.13, 3.31)	.016	2.31 (1.28, 4.20)	.006						
	IVC	3.15 (1.83, 5.42)	<.001	3.88 (2.13, 7.06)	<.001						

Abbreviations: AIC, akaike information criterion; AJCC, the American joint committee on cancer; BIC, bayesian information criterion; CSS, cancer-specific survival; OS, overall survival.

CSS of the patients in stage T1-3aN1M0 were significantly worse than those in stage T1-3aN0M0 (OS: log-rank test p = .048, CSS: log-rank test p = .013), while they were not different from those in stage T3b-T4bN0/N1M0 (OS: log-rank test p = .620, CSS: log-rank test p = .498). These evidences supported the reclassification of T1-3aN1M0 in the AJCC-v7 to the IVB stage in the AJCC-v8.

In line with this, using the Cox proportional hazards model with stage IVA as a reference, the adjusted HR for OS of patients staged IVB and IVC according to the AJCC-v8 staging system was both significantly higher than those in the AJCC-v7 (IVB, AJCC-v8 vs. AJCC-v7, HR: 1.93 vs. 1.47; IVC, AJCC-v8 vs. AJCC-v7, HR: 3.15 vs. 2.41) (Table 3). Moreover, there was no statistical difference in the risk of all-cause mortality for the ATC patients in stages IVA and IVB according to the AJCC-v7 (HR, 1.47, 95% CI, 0.96-2.25; p = .079). Noteworthy, the AJCC-v8 had higher C-index (0.60 vs. 0.59) and lower AIC (2728 vs. 2732) and BIC (2732 vs. 2735) compared with the AJCC-v7 for OS (Table 3). Similarly, AJCC-v8 also showed improved performance in predicting CSS. These data indicated that AJCC-v8 had better model performance than AJCC-v7 in predicting the prognosis of ATC patients.

4 | DISCUSSION

Our study made an in-depth exploration of the association between lymph node status and survival of patients with ATC for the first time. The results showed that LNM was independently associated with worse OS and CSS in ATC patients, while the mortality risk showed no significant difference between patients with central LNM (N1a) and those with lateral LNM (N1b). On the basis of these evidences, our study demonstrates that AJCC-v8 presents better predictive ability for the prognosis of patients with ATC than the predecessor, AJCC-v7. As ATC is a rare disease with terrible prognosis, there are limited researches on its prognostic evaluation. Our work based on the SEER database provides evidences for the application of AJCC-v8 in prognostic evaluation for patients with ATC and contributes to the improved understanding of LNM in ATC, which may be conducive to the diagnosis and precise treatment of ATC in clinical practice.

Notably, LNM was not associated with a poor prognosis for patients with ATC in previous studies based on the K–M method[10] or multivariate Cox model[9,11]. A study based on ATC Research Consortium of Japan (ATCCJ) database (between 1995 and 2008 year) showed that although the mortality of patients with LNM was lower than those without LNM, LNM remained unrelated to the survival of ATC through univariate cox analysis.[11] Nevertheless, another recent study based on the ATCCJ database (between 2009 and 2019 year) showed that N1 stage was a risk factor for the mortality of ATC (HR: 1.2, 95% CI, 1.0–1.5; p = .030) through univariate cox model, but had no concern with survival when adjusted with age, gender, T stage and M stage.[9] In contrast, we found that LNM was a significant and independent risk factor for poor survival of ATC based on SEER database. The difference may be partly attributed to that

tumour characteristics, and treatment information such as lymph node resection was included as adjustment factors when evaluating the association between LNM and survival of ATC in our study. Nevertheless, in the current study, although LNM has been shown to be related to greater risk of death, the magnitude of this increase remains relatively small after adjustment. The subgroup analysis in our research on the association of LNM with OS and CSS clarified that LNM was correlated with poor prognosis in elderly ATC patients with localized and moderate-sized (4.1–6 cm) tumour. These data suggested that the impact of LNM on survival might only be significant in some subgroups. It can be speculated that combining the interactive effects of age, tumour invasion, tumour size and lymph nodes in AJCC staging system may improve the accuracy of survival prediction for ATC. Furthermore, taking into account that the poor prognosis of ATC patients and the fact of high incidence of surgical complications may further destroy the patient's quality of life, the indications of lymph node resection and the method of surgery need further research.

Notably, our study was the first to evaluate the prognosis of ATC patients staged N1a and N1b, and found that there was no significant difference in survival between the two groups. Consistent with this evidence, N1a and N1b are not used as staging element in either AJCC-V8 or AJCC-V7. Based on the above evidence, it can be inferred that including LNM as a staging element may improve the survival prediction ability of AJCC-v8. In consistence with this, there was a significant increase in the HRs for the OS and CSS for patients in stages IVB and IVC, in reference to the IVA stage in our study population. Meanwhile, we demonstrated that the survival of migration patients (T1-3aN1M0) was significantly different from that of patients staged IVA but similar to that of patients staged IVB. Although there were only 13 patients who had experienced a stage migration according to AJCC-v8, 11 cases among them were followed up to the death. We believe that this result has some statistical value and credibility. In fact, because of the small number of patients with stage migration in the entire study population, although the C-index, AIC and BIC of AJCC-V8 were improved, the improvement was not remarkable. Of note, the C-index of AJCC-v8 was only 0.60 in our study, indicating its insufficient prognostic predictive performance. More researches on the prognostic evaluation of ATC are needed for constructing the AJCC system.

Finally, as our analysis was based on the retrospective data from SEER, there were some limitations. As the diagnosis of ATC is often difficult and diagnostic variation often occurs, we brought thyroid cancers with ICD-O-3 code of 8020–8035 into our study, which resulted in a small number of poorly differentiated carcinoma or squamous cell carcinoma patients being included in the study population. At the same time, the number of cases included in the analysis was not big enough after the relatively strict exclusion criteria were applied. Thus, further studies with appropriate design and adequate power are required to definitively clarify that LNM can increase the mortality risk of ATC, and to robustly investigate the magnitude of the increase in mortality risk.

5 | CONCLUSION

Our study demonstrates, for the first time, that LNM is an independent risk factor for poor survival in patients with ATC, while the effects of N1a and N1b on the prognosis prediction are indistinguishable. The AJCC-v8 with the revision that reclassifies patients with LNM into higher stages is more accurate for predicting mortality than the AJCC-v7. As ATC remains a clinical challenge to date, there is a need to develop better in-depth research into the diagnostic and therapeutic approaches to this disease.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHORS CONTRIBUTIONS

H.Z and Y.-C.Z. designed the study, collected and analysed data, and wrote the manuscript. Y.-C.Z. and Q.W. performed the statistical analysis. L.W. and S.S. edited the manuscript, provided valuable suggestions for study and supervised the study. All authors have approved the final version of this paper.

DATA AVAILABILITY STATEMENT

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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