Original Article

Nomogram predicts risk and prognostic factors for lung metastasis of anaplastic thyroid carcinoma: a retrospective study in the Surveillance Epidemiology and End Results (SEER) database

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Background: Lung metastasis (LM) is a frequent occurrence in patients with anaplastic thyroid cancer (ATC) and is often associated with a poor prognosis. However, there is currently a lack of specific research focusing on the diagnostic and prognostic evaluation of LM in ATC patients using nomograms. Consequently, the establishment of effective predictive models holds significant importance in providing guidance for clinical practice.

Methods: We screened patients from Surveillance Epidemiology and End Results (SEER) database between 2000 and 2018. To identify independent risk factors for LM in patients with ATC, we conducted univariate and multivariate logistic regression analyses. We also conducted univariate and multivariate Cox proportional hazards regression analyses to identify independent prognostic factors for ATC patients with LM. Based on these analyses, we developed two novel nomograms. The performance of the nomograms was assessed using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

Results: A cohort of 540 ATC patients was enrolled in the study, among whom 181 patients (33.5%) were identified with LM at the time of initial diagnosis. The independent risk factors for LM in patients with ATC included tumor size, extent of surgery, lateral cervical lymph node metastasis, and radiotherapy. Furthermore, tumor size, extent of surgery, radiotherapy, and chemotherapy were identified as independent factors influencing the prognosis of ATC patients with LM. The accuracy of the two nomograms in predicting the occurrence and prognosis of LM in ATC patients was confirmed through the analysis of ROC curves, calibration, DCA curves, and Kaplan-Meier (K-M) survival curves on both the training and validation sets.

Conclusions: The two nomograms are highly accurate in predicting LM in patients with ATC and in forecasting patient outcomes for patients with lung metastases. Consequently, they offer valuable support for personalized clinical decision-making in future clinical practice.

Keywords: Anaplastic thyroid cancer (ATC); lung metastasis (LM); Surveillance Epidemiology and End Results database (SEER database); nomogram

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Introduction

Anaplastic thyroid cancer (ATC) is a rare form of thyroid tumor and is widely regarded as one of the most aggressive malignancies. Over the past three decades, the incidence of ATC has remained stable, accounting for only 0.2% of all thyroid tumors, with a median survival time of 3 to 6 months (1-5). Compared to other pathological subtypes of thyroid cancer, ATC is characterized by greater invasiveness, making it more prone to local invasion and metastasis to regional lymph nodes and distant sites (6). ATC is distinguished by approximately 10% of tumor cases being localized solely within the thyroid gland, whereas 40% of patients present with extrathyroidal infiltration and lymph node metastasis, and the remaining patients demonstrate distant metastasis (7). The most common sites of distant metastasis in ATC are the lungs, followed by other organs such as bones and brain (8,9). Once distant metastasis occurs, it indicates a poorer prognosis for the patients. However, our current knowledge is limited regarding the correlation between the clinical and pathological features of ATC and LM. Additionally, no specific prognostic models have been developed to predict the occurrence of LM in ATC or to assess the prognosis of ATC patients with LM. Nomograms play a crucial role in managing cancer prognosis and recurrence by simplifying complex statistical prediction models into a single numerical estimate, accurately reflecting the probability of events such as death or recurrence while considering the unique circumstances of individual patients (10,11). In the field of cancer management, nomograms have emerged as a superior alternative to traditional tumor-node-metastasis (TNM) staging systems for a wide variety of cancers, thereby establishing a new standard in clinical practice (12-14). Therefore, nomograms are an excellent choice for achieving our intended purpose. In this study, we employed the Surveillance Epidemiology, and End Results (SEER) database to evaluate the incidence, risk factors, and prognosis of LM in ATC. Additionally, we developed two nomograms, one for predicting LM in ATC patients and another for predicting the overall survival (OS) of ATC patients with concurrent LM. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1195/rc).

Highlight box

Key findings

- This study developed two precise nomograms to predict lung metastasis (LM) of anaplastic thyroid carcinoma occurrence and prognosis. Tumor size, surgery extent, radiotherapy, and chemotherapy were identified as independent factors influencing the prognosis of anaplastic thyroid cancer (ATC) patients with LM.

What is known and what is new?

- LM is a frequent occurrence in patients with ATC and is often associated with a poor prognosis.
- There is currently a lack of specific research focusing on the diagnostic and prognostic evaluation of LM in ATC patients using nomograms.

What is the implication, and what should change now?

- These nomograms enhance prognosis-based decision making for each patient, which is essential to improve patient outcomes and provides valuable guidance for clinical decision making.

Methods

Patient selection

This study is an observational retrospective cohort study. The current study data of ATC patients were extracted from the SEER database from 2000 to 2018, which comprises data from 18 cancer registries. The SEER program, established in 1973 and supported by the National Cancer Institute (NCI) in the United States, encompasses information on survival characteristics and the incidence of malignant tumors from approximately 28% of the population, as reported by cancer registries nationwide (15). The data utilized in this study were obtained by downloading them from the SEER*Stat software version 8.4.1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Inclusion criteria were as follows: (I) patients with histologically confirmed ATC, who were diagnosed according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), with diagnostic codes 8021/3 and 8020/3; (II) demographic variables, including age, sex, marital status and race were available; (III) clinical pathological information, including the primary tumor extent of invasion, lymph node metastasis, surgical intervention, presence of LM, treatment with radiotherapy and chemotherapy, as well as tumor size, were all available for analysis. Patients with non-pathological diagnosis, marriage status unknown, brain, lung, liver and bone metastasis unknown, race of the patient unknown, radiotherapy or chemotherapy unknown,

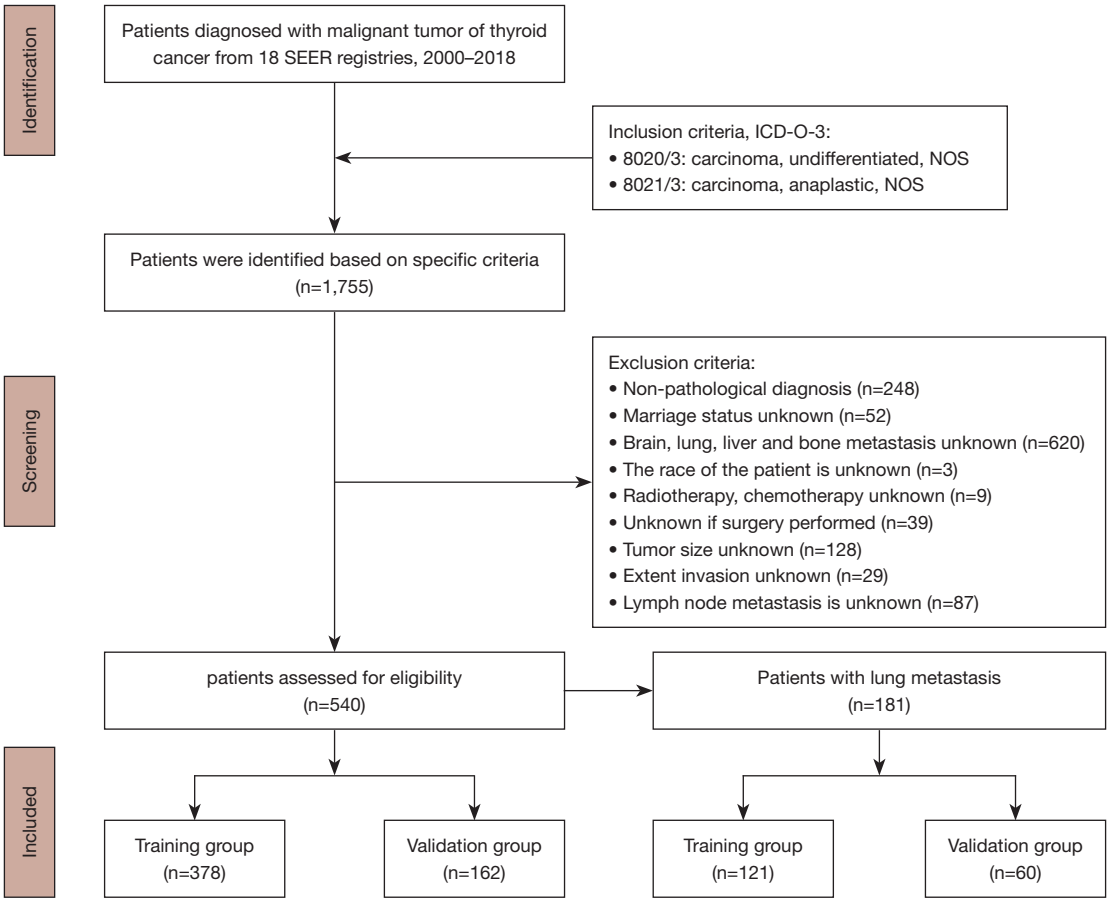

Figure 1 Flowchart depicting the process of patient selection. SEER, Surveillance Epidemiology, and End Results; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; NOS, not otherwise specified.

unknown if surgery performed, tumor size unknown, extent invasion unknown, lymph node metastasis unknown, lost to follow-up, or incomplete medical records were excluded during the patient's selection process (*Figure 1*).

Data collection

In this study, after excluding ineligible cases, a total of 540 patients diagnosed with ATC were included in the current study, out of whom 181 patients exhibited LM. The entire patient cohort was utilized to establish a diagnostic cohort for investigating the risk factors associated with LM and developing a predictive nomogram. In addition, a prognostic cohort consisting of 181 ATC patients with LM, who had detailed treatment information including surgery, chemotherapy, and radiation therapy, was established. This cohort was utilized to construct an innovative prognostic nomogram for evaluating the prognosis of patients with LM. The patients in the diagnostic cohort were randomly divided into a training set (70%) and a validation set (30%) in a 7:3 ratio. The prognostic cohort consisted of patients with LM selected from the corresponding sets of the diagnostic cohort, both in the training and validation sets. The training set in each cohort was utilized to develop the nomogram, while the validation set was employed to evaluate its performance. In addition, we investigated prognostic factors for ATC patients with LM through survival analyses. The primary outcome in this analysis was OS, which was defined as the time period between the date of diagnosis and the date of death from any cause.

Statistical analysis

In this study, all statistical analyses were conducted using

SPSS 26.0 and R software (R Foundation, Vienna, Austria, version 4.2.2, http://www.r-project.org). Univariate and multifactor logistic regression analyses, as well as univariate and multifactor Cox regression analyses, were performed using SPSS. P<0.05 (bilateral) was considered statistically significant. The distribution of variables between the two sets was compared using the Chi-squared test or Fisher's exact test. When the minimum theoretical frequency is greater than 5, the Chi-squared test is used. If the P value of the Chi-squared test is near 0.05, the Fisher's exact test is used instead. When the minimum theoretical frequency is less than 5, Fisher's exact test is used directly. The R software packages "regplot", "pROC", "ggDCA", "survival", "ggplot2", "rms", "survminer", and "foreign" were utilized to construct and generate nomograms, receiver operating characteristic (ROC) curves, calibration curves, decision curve analysis (DCA), and conduct Kaplan-Meier (K-M) survival curves. In the diagnostic cohort, we conducted univariate and multivariate logistic analyses to identify independent risk factors associated with LM in ATC patients. A diagnostic nomogram was developed using the independent risk factors, and its performance was evaluated through ROC curve analysis, including calculation of the area under the curve (AUC). Additionally, the performance of the nomogram was evaluated using calibration curves and DCA. To identify independent prognostic factors, we conducted univariate and multivariate Cox analysis. Based on these independent predictors, a prognostic nomogram was developed to predict the OS of ATC patients with LM. Individual risk scores were calculated using the formula derived from the nomogram. Moreover, time-dependent ROC curves were generated to evaluate the nomogram's predictive performance across different time points. Calibration curves and DCA were plotted to evaluate the nomogram's performance. ATC patients with LM were divided into high-risk and low-risk groups based on their median risk score. K-M survival curves, with the log-rank test, were employed to evaluate and compare the OS between these two groups.

Results

Baseline clinical characteristics of patients

In this study, a cohort of 540 patients diagnosed with ATC were included, with 378 individuals allocated to the training set and 162 individuals assigned to the validation set for stratification and analysis. In the cohort of 540 cases of ATC, 181 patients (33.5%) experienced LM, while 426 (78.9%) cases were 60 years old or above, there were 217 male patients and 323 female patients, resulting in a male-to-female ratio of 1:1.49. It was found that individuals of white people accounted for 81.9% of the total population, 460 cases (85.2%) exhibited external thyroid invasion, 104 cases (19.3%) presented with invasion of the trachea, 86 cases (15.9%) displayed central lymph node metastasis, 233 cases (43.1%) had lymph node metastasis in the lateral neck region. In terms of treatment, surgery was performed in 343 cases (63.5%), radiation therapy was administered in 338 cases (62.6%), and chemotherapy was given in 265 cases (49.1%). As for tumor size, tumors larger than 6cm accounted for 330 cases (61.1%). Furthermore, the Chi-squared test was conducted to assess the randomness of the deviation, and the results indicated a complete randomization (*Table 1*).

Univariate and multivariate logistic analyses of the risk factors of LM

In order to investigate the potential clinical factors related to the risk of LM in ATC, a logistic analysis was conducted. In this study, univariate logistic analysis was conducted on 12 potential factors, revealing five variables significantly associated with LM, including tumor size, surgery extent, central lymph node metastasis, lateral cervical lymph node metastasis, and radiotherapy. Furthermore, multivariate logistic regression analysis demonstrated that tumor size, surgery extent, lateral cervical lymph node metastasis, and radiotherapy were independent risk predictors for LM in ATC patients (*Table 2*).

Diagnostic nomogram establishment and validation

Based on four independent predictors, a novel nomogram was developed for predicting lung metastases in ATC patients (*Figure 2A*). Following that, ROC curves were generated to assess the discriminative performance of the nomogram, with AUC values of 0.680 obtained for the training sets, indicating favorable discrimination (*Figure 2B*). Meanwhile, a high level of consistency was observed between the observed outcomes and the predicted outcomes within the calibration curve (*Figure 2C*). Additionally,

Table 1 Baseline clinical characteristics of patients diagnosed as ATC

Characteristics	Training group (n=378), n (%)	Validation group (n=162), n (%)	Overall (n=540), n (%)	χ^2	P value
Age at diagnosis (years)				0.724	0.627
<60	84 (22.2)	30 (18.5)	114 (21.1)		
≥60	294 (77.8)	132 (81.5)	426 (78.9)		
Sex				3.241	0.166
Female	236 (62.4)	87 (53.7)	323 (59.8)		
Male	142 (37.6)	75 (46.3)	217 (40.2)		
Race				2.98	0.811
White	307 (81.2)	135 (83.3)	442 (81.9)		
Asian	43 (11.4)	15 (9.3)	58 (10.7)		
Black	26 (6.9)	9 (5.6)	35 (6.5)		
Other	2 (0.5)	3 (1.9)	5 (0.9)		
Marital status				0.454	0.743
Yes	227 (60.1)	103 (63.6)	330 (61.1)		
No	151 (39.9)	59 (36.4)	210 (38.9)		
Size (cm)				0.454	0.743
≤6	143 (37.8)	67 (41.4)	210 (38.9)		
>6	235 (62.2)	95 (58.6)	330 (61.1)		
Surgery				2.083	0.305
Yes	248 (65.6)	95 (58.6)	343 (63.5)		
No	130 (34.4)	67 (41.4)	197 (36.5)		
External thyroid invasion				3.930	0.107
Yes	330 (87.3)	130 (80.2)	460 (85.2)		
No	48 (12.7)	32 (19.8)	80 (14.8)		
Tracheal invasion				2.545	0.23
Yes	80 (21.2)	24 (14.8)	104 (19.3)		
No	298 (78.8)	138 (85.2)	436 (80.7)		
Central lymph node metastasis				0.111	0.899
Yes	62 (16.4)	24 (14.8)	86 (15.9)		
No	316 (83.6)	138 (85.2)	454 (84.1)		
Lateral cervical lymph node metastasis				0.013	0.978
Yes	162 (42.9)	71 (43.8)	233 (43.1)		
No	216 (57.1)	91 (56.2)	307 (56.9)		
Lung metastasis				1.070	0.526
Yes	121 (32.0)	60 (37.0)	181 (33.5)		
No	257 (68.0)	102 (63.0)	359 (66.5)		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Training group (n=378), n (%)	Validation group (n=162), n (%)	Overall (n=540), n (%)	χ^2	P value
Radiotherapy				0.136	0.897
Present	239 (63.2)	99 (61.1)	338 (62.6)		
Absent	139 (36.8)	63 (38.9)	202 (37.4)		
Chemotherapy				0.141	0.896
Yes	188 (49.7)	77 (47.5)	265 (49.1)		
No	190 (50.3)	85 (52.5)	275 (50.9)		
Status				1.497	0.406
Alive	77 (20.4)	25 (15.4)	102 (18.9)		
Dead	301 (79.6)	137 (84.6)	438 (81.1)		

ATC, anaplastic thyroid cancer.

Table 2 Univariate and multivariate logistic regression analyses were performed to explore the correlation between clinical variables and the occurrence of lung metastasis in ATC

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age at diagnosis (years)						
<60	Reference			–	–	–
≥60	1.118	0.774–1.631	0.621	–	–	–
Sex						
Female	Reference			–	–	–
Male	1.374	1.013–1.862	0.085	–	–	–
Race						
Asian	Reference			–	–	–
White	0.486	0.305–0.775	0.011	–	–	–
Black	0.559	0.266–1.147	0.188	–	–	–
Other	1.607	0.339–8.821	0.617	–	–	–
Marital status						
No	Reference			–	–	–
Yes	1.395	1.022–1.913	0.079	–	–	–
Size (cm)						
≤6	Reference			Reference		
>6	1.676	1.223–2.310	0.007	1.428	1.022–2.002	0.038
Surgery extent						
No	Reference			Reference		
Yes	0.311	0.226–0.424	<0.001	0.373	0.268–0.517	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
External thyroid invasion						
No	Reference			–	–	–
Yes	1.392	0.903–2.194	0.218	–	–	–
Tracheal invasion						
No	Reference			–	–	–
Yes	0.95	0.647–1.392	0.843	–	–	–
Central lymph node metastasis						
No	Reference			Reference		
Yes	0.511	0.318–0.796	0.015	0.859	0.509–1.421	0.626
Lateral cervical lymph node metastasis						
No	Reference			Reference		
Yes	2.098	1.548–2.848	<0.001	1.557	1.101–2.206	0.035
Radiotherapy						
Absent	Reference			Reference		
Present	0.491	0.361–0.668	<0.001	0.532	0.384–0.735	0.001
Chemotherapy						
No	Reference			–	–	–
Yes	0.823	0.609–1.112	0.288	–	–	–

ATC, anaplastic thyroid cancer; OR, odds ratio; CI, confidence interval.

the outcomes of the DCA provided clear evidence of the superior performance of the diagnostic nomogram in clinical practice, as exemplified by the results depicted in *Figure 2D*. The ROC analysis of the validation set showed that the AUC value of the nomogram was 0.713, indicating good discriminative ability of the model in the validation set (*Figure 2E*). The calibration curve in the validation set demonstrated the best consistency between nomogram predictions and actual observations (*Figure 2F*). Furthermore, DCA in the validation set also confirmed the favorable performance of the nomogram model in clinical practice (*Figure 2G*). Further, ROC curves were constructed for each of the independent predictor variables, emphasizing their importance in predicting LM risk. The results presented in *Figure 3* highlight a notable superiority of the nomogram over individual independent predictors. Remarkably, the nomogram displayed a higher AUC compared to each individual independent variable in both the training and validation set cohorts. The significant disparity in AUC values indicates a notable benefit in prediction accuracy when utilizing the nomogram instead of solely relying on individual independent predictors.

Univariate and multivariate Cox analyses of the risk factors of OS

This study utilized a cohort of 181 eligible ATC patients with lung metastases to investigate prognostic factors. Among them, a total of 121 patients were included in the training cohort, while the remaining 60 patients were included in the validation cohort. According to the data presented in *Table 3*, a total of 82 patients (45.3%) underwent surgery, 83 patients (45.9%) received chemotherapy, and 93 patients (51.4%) received

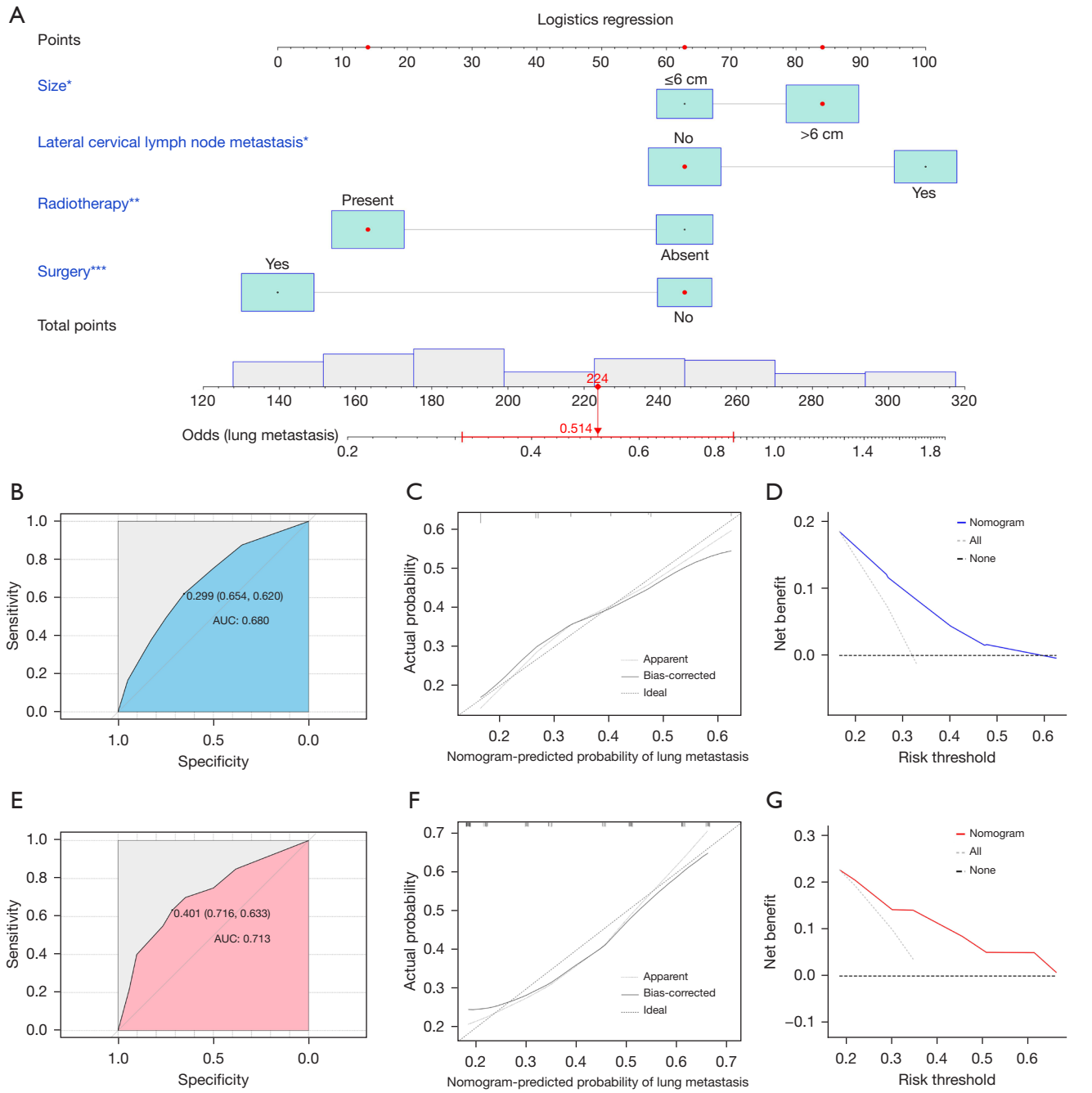

Figure 2 Developing a diagnostic nomogram and validating. (A) Nomogram to estimate the risk of lung metastasis in patients with ATC. (B-D) The ROC curves (B), calibration curves (C), and DCA (D) of the training set cohort. (E-G) The ROC curves (E), calibration curves (F), and DCA (G) of the validation set cohort. *, P<0.05; **, P<0.01; ***, P<0.001. AUC, area under the curve; ATC, anaplastic thyroid cancer; ROC, receiver operating characteristic; DCA, decision curve analysis.

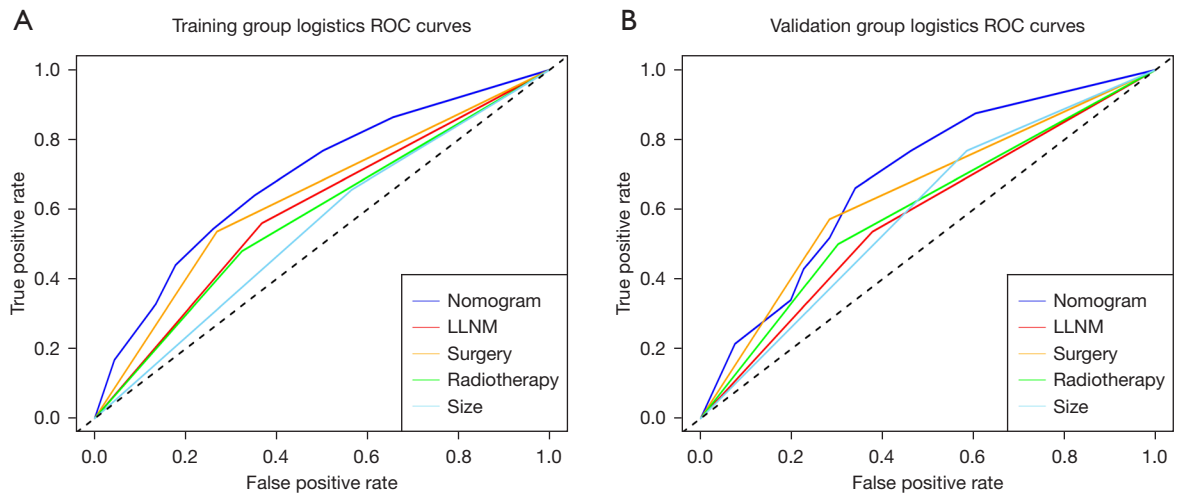

Figure 3 The area under the ROC curves was compared between the nomogram and all independent factors, which included lateral cervical lymph node metastasis, surgery extent, radiotherapy, and tumor size, in both the training set cohort (A) and validation set cohort (B). ROC, receiver operating characteristic; LLNM, lateral cervical lymph node metastasis.

Table 3 Baseline clinical characteristics of ATC patients with lung metastases

Characteristics	Training group (n=121), n (%)	Validation group (n=60), n (%)	Overall (n=181), n (%)	χ^2	P value
Age at diagnosis (years)				0.926	0.511
<60	27 (22.3)	9 (15.0)	36 (19.9)		
≥60	94 (77.7)	51 (85.0)	145 (80.1)		
Sex				1.875	0.311
Female	71 (58.7)	28 (46.7)	99 (54.7)		
Male	50 (41.3)	32 (53.3)	82 (45.3)		
Race				2.082	0.912
White	89 (73.6)	49 (81.7)	138 (76.2)		
Asian	22 (18.2)	6 (10.0)	28 (15.5)		
Black	8 (6.6)	4 (6.7)	12 (6.6)		
Other	2 (1.7)	1 (1.7)	3 (1.7)		
Marital status				0.331	0.759
Yes	78 (64.5)	42 (70.0)	120 (66.3)		
No	43 (35.5)	18 (30.0)	61 (33.7)		
Size (cm)				0.001	0.982
≤6	38 (31.4)	18 (30.0)	56 (30.9)		
>6	83 (68.6)	42 (70.0)	125 (69.1)		
Surgery extent				2.205	0.259
Yes	60 (49.6)	22 (36.7)	82 (45.3)		
No	61 (50.4)	38 (63.3)	99 (54.7)		

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Training group (n=121), n (%)	Validation group (n=60), n (%)	Overall (n=181), n (%)	χ^2	P value
External thyroid invasion				2.401	0.201
Yes	110 (90.9)	49 (81.7)	159 (87.8)		
No	11 (9.1)	11 (18.3)	22 (12.2)		
Tracheal invasion				1.254	0.417
Yes	26 (21.5)	8 (13.3)	34 (18.8)		
No	95 (78.5)	52 (86.7)	147 (81.2)		
Central lymph node metastasis				0.383	0.681
Yes	11 (9.1)	8 (13.3)	19 (10.5)		
No	110 (90.9)	52 (86.7)	162 (89.5)		
Lateral cervical lymph node metastasis				0.042	0.936
Yes	68 (56.2)	32 (53.3)	100 (55.2)		
No	53 (43.8)	28 (46.7)	81 (44.8)		
Radiotherapy				0.176	0.846
Present	64 (52.9)	29 (48.3)	93 (51.4)		
Absent	57 (47.1)	31 (51.7)	88 (48.6)		
Chemotherapy				0.097	0.895
Yes	54 (44.6)	29 (48.3)	83 (45.9)		
No	67 (55.4)	31 (51.7)	98 (54.1)		
Status				1.694	0.294
Alive	15 (12.4)	3 (5.0)	18 (9.9)		
Dead	106 (87.6)	57 (95.0)	163 (90.1)		

ATC, anaplastic thyroid cancer.

radiotherapy. Statistical analysis using the Chi-squared test and Fisher's exact test revealed that there were no significant differences observed in any of the variables between the training set and the validation set. In the univariate Cox proportional hazards regression analysis, tumor size, surgery extent, radiotherapy, and chemotherapy were identified as factors related to OS. After adjusting for confounding variables through multivariate Cox proportional hazards regression analysis, tumor size >6 cm, absence of surgery, absence of radiotherapy, and absence of chemotherapy were confirmed as independent prognostic factors in patients with ATC and LM (*Table 4*).

Prognostic nomogram establishment and validation

A prognostic nomogram was developed for ATC patients with LM, based on four independent prognostic factors (*Figure 4*). The calibration curves of the nomogram demonstrated excellent agreement between the predicted probability of 2-, 4-, and 6-month OS and the actual outcome in the training set cohort (*Figure 5A-5C*). These curves serve as visual representations of the nomogram's performance in accurately predicting OS at different time points. In addition, the DCA curves in the training set demonstrated the favorable performance of the nomogram in clinical practice, as depicted in *Figure 5D-5F*. The

Table 4 Univariate and multivariate Cox analyses in ATC patients with lung metastases

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age at diagnosis (years)						
<60	Reference			–	–	–
≥60	1.349	0.917–1.984	0.128	–	–	–
Sex						
Female	Reference			–	–	–
Male	0.782	0.569–1.075	0.131	–	–	–
Race						
Asian	Reference			–	–	–
White	1.155	0.746–1.791	0.516	–	–	–
Black	2.025	0.961–4.269	0.063	–	–	–
Other	1.167	0.274–4.958	0.834	–	–	–
Marital status						
No	Reference			–	–	–
Yes	0.845	0.606–1.179	0.323	–	–	–
Size (cm)						
≤6	Reference			Reference		
>6	1.447	1.032–2.031	0.032	1.412	0.998–1.996	0.041
Surgery extent						
No	Reference			Reference		
Yes	0.579	0.422–0.795	<0.001	0.665	0.481–0.921	0.014
External thyroid invasion						
No	Reference			–	–	–
Yes	0.865	0.539–1.388	0.548	–	–	–
Tracheal invasion						
No	Reference			–	–	–
Yes	0.678	0.439–1.049	0.081	–	–	–
Central lymph node metastasis						
No	Reference			–	–	–
Yes	1.071	0.644–1.778	0.793	–	–	–
Lateral cervical lymph node metastasis						
No	Reference			–	–	–
Yes	1.118	0.817–1.531	0.484	–	–	–

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Radiotherapy						
Absent	Reference			Reference		
Present	0.509	0.372–0.695	<0.001	0.616	0.442–0.859	0.004
Chemotherapy						
No	Reference			Reference		
Yes	0.411	0.297–0.566	<0.001	0.502	0.356–0.707	<0.001

ATC, anaplastic thyroid cancer; HR, hazard ratio; CI, confidence interval.

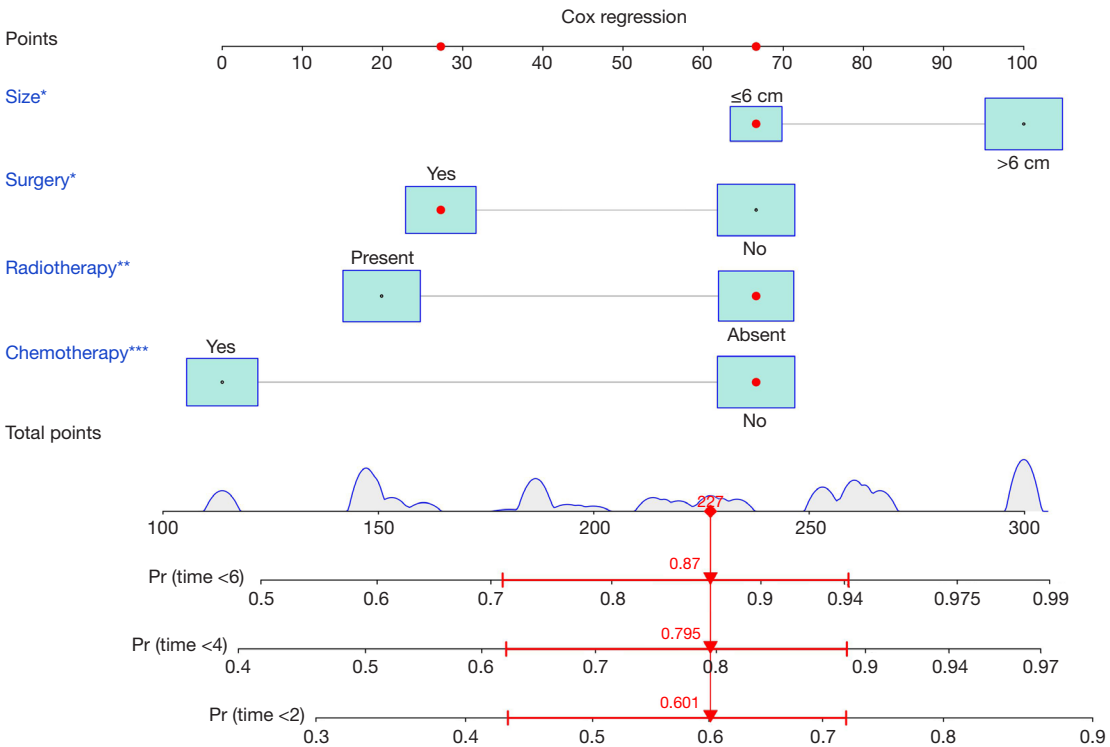

Figure 4 Nomogram to predict the OS of ATC patients with lung metastases. *, P<0.05; **, P<0.01; ***, P<0.001. Pr, probability; OS, overall survival; ATC, anaplastic thyroid cancer.

calibration curves of the nomogram in the validation cohort exhibited robust concordance between the anticipated probabilities of 2-, 4-, and 6-month OS and the observed outcomes (*Figure 6A-6C*). Moreover, the training set's DCA curve corroborates the nomogram's efficacy in real-world clinical settings, as illustrated in *Figure 6D-6F*. Furthermore, the ROC analysis revealed that the nomogram exhibited good discrimination in predicting OS of ATC patients with LM. Specifically, in the training set, the AUC for the nomogram at 2, 4, and 6 months was 0.773, 0.806, and 0.816, respectively (*Figure 7A*). Similarly, in the validation set, the AUC for the nomogram at the same time intervals

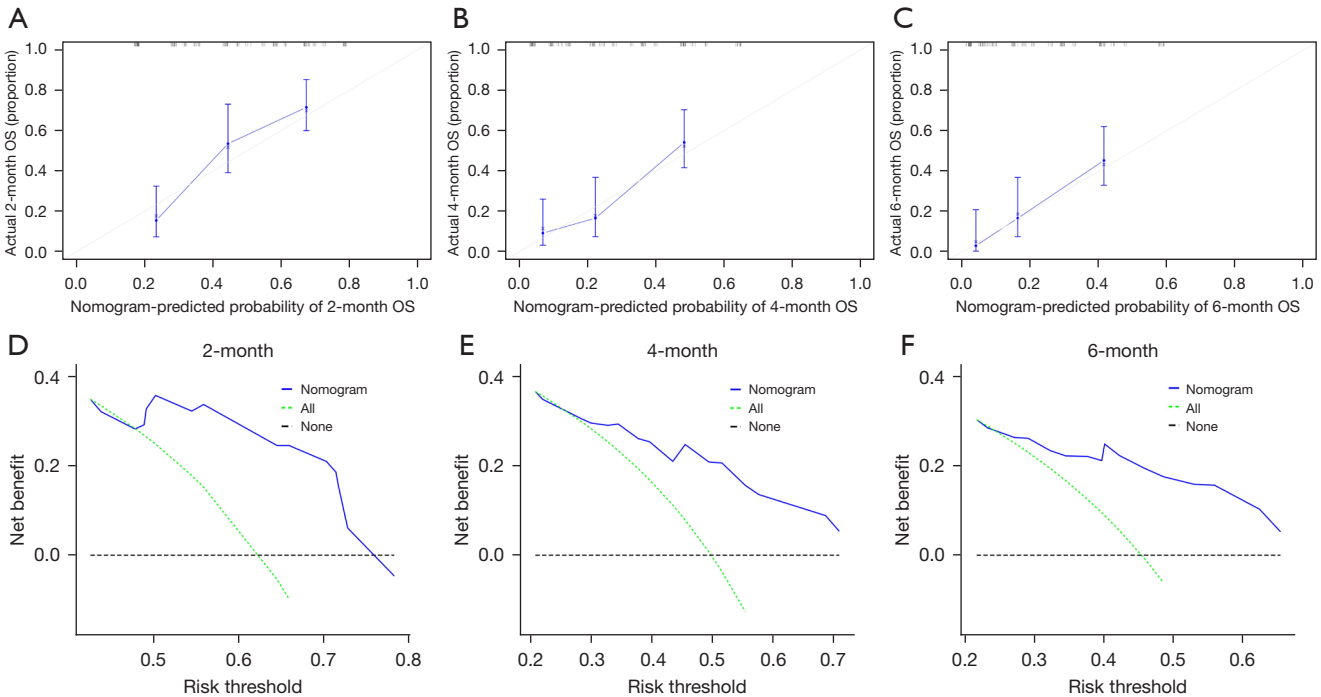

Figure 5 The calibration curves of the prognostic nomogram for the 2 (A), 4 (B), and 6 (C) months in the training set cohort, and the DCA of the prognostic nomogram for the 2 (D), 4 (E), and 6 (F) months in the training set cohort. OS, overall survival; DCA, decision curve analysis.

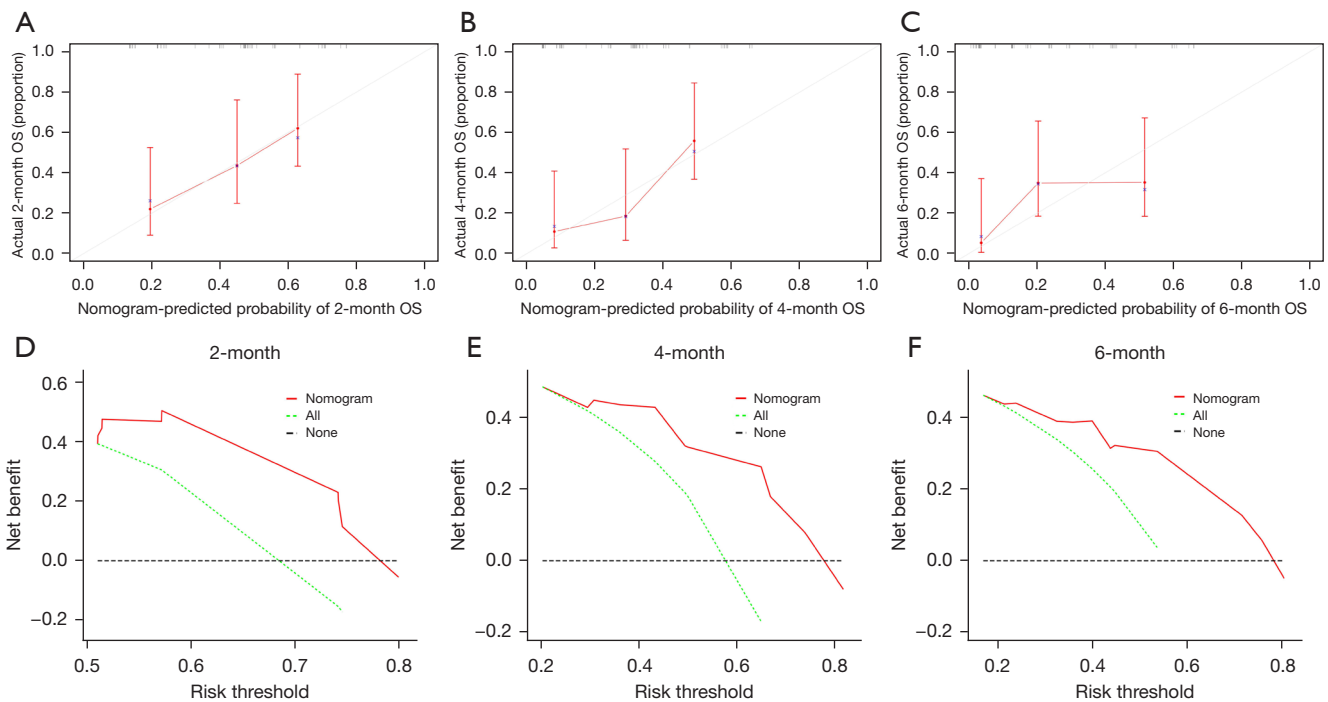

Figure 6 The calibration curves of the prognostic nomogram for the 2 (A), 4 (B), and 6 (C) months in the validation set cohort, and the DCA of the prognostic nomogram for the 2 (D), 4 (E), and 6 (F) months in the validation set cohort. OS, overall survival; DCA, decision curve analysis.

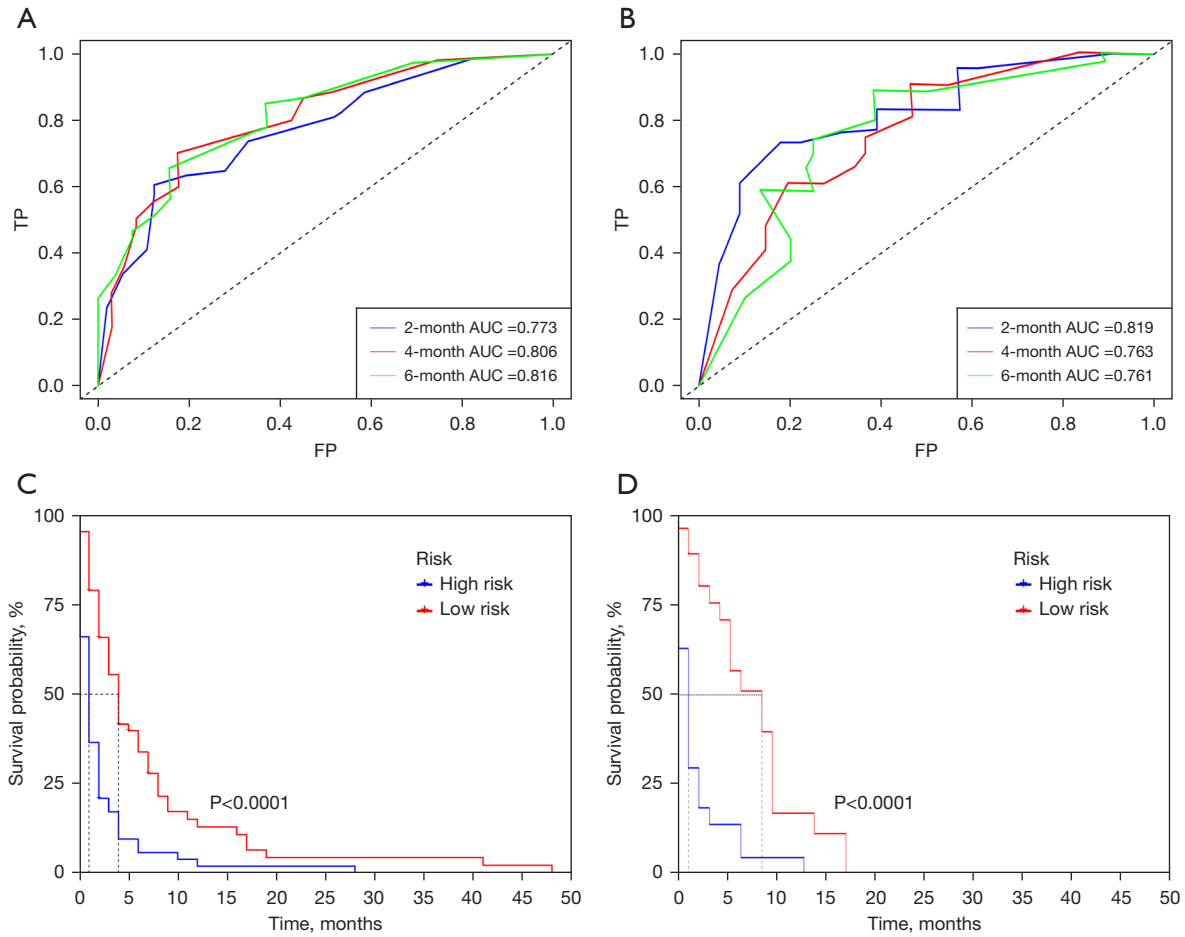

Figure 7 Time-dependent ROC curve of 2, 4, and 6 months in the training set cohort (A) and the validation set cohort (B), and the Kaplan-Meier survival curves of the training set cohort (C) and the validation set cohort (D). TP, true positive; FP, false positive; AUC, area under the curve; ROC, receiver operating characteristic.

was 0.819, 0.763, and 0.761, respectively (*Figure 7B*). These results further validate the nomogram's predictive accuracy and discrimination ability. Moreover, the K-M survival curves clearly illustrate that patients classified in the high-risk group had a significantly poorer prognosis compared to patients classified in the low-risk group (P<0.0001) (*Figure 7C*,*7D*). The prognostic nomogram demonstrates a notable positive net benefit across a wide spectrum of mortality risks, underscoring its considerable clinical utility in forecasting OS among ATC patients with LM.

Discussion

ATC is a rare malignant tumor of the thyroid gland, characterized by its invasive nature and high mortality rate (16). According to previous literature reports, approximately half of ATC patients present with evidence of metastatic disease at the time of diagnosis, and around 25% of patients experience metastasis during the course of their illness (17). The lungs are the most common site of metastasis in ATC, ultimately leading to respiratory failure, which is a crucial factor contributing to patient mortality (9,18). Currently, the primary treatment modalities for ATC include surgery, radiotherapy, chemotherapy, and other comprehensive approaches (19). However, the overall prognosis remains challenging and not optimistic (20). Therefore, the identification of effective risk and prognostic factors for ATC patients with LM is of paramount

importance. This will not only enable early-stage diagnosis and facilitate early prevention but also contribute to the accurate evaluation of the prognosis for these patients. In this study, we developed diagnostic and prognostic nomograms by analyzing a large dataset. These nomograms were designed to predict the risk of LM in ATC patients and the OS of ATC patients with LM, respectively. Through obtaining data on the corresponding variables for each ATC patient on the nomograms, a cumulative score can be calculated. This facilitates the identification of the risk of LM on the diagnostic chart, enabling the recognition of high-risk individuals and guiding early interventions in clinical practice. Likewise, the prognostic nomogram can be employed to assess the prognosis of ATC patients with LM. The implementation of this tool will simplify its integration into clinical practice, enabling physicians to determine the optimal treatment strategy for their patients with enhanced convenience and precision. To the best of our knowledge, our research stands as the first multicenter and comprehensive retrospective study in the field, dedicated to developing nomogram models for predicting the risk and prognosis of LM in patients diagnosed with ATC.

Currently, there is limited research on the risk factors for LM in ATC, and there is a lack of large-scale population-based studies. This may be largely due to the low incidence rate of ATC, which contributes to the scarcity of available data. In this study, we integrated recent extensive samples containing comprehensive clinical information obtained from the SEER database. Our findings revealed that the prevalence of LM was determined to be 33.5%. We identified four significant predictors for LM in ATC patients, which include tumor size, extent of surgery, presence of lateral cervical lymph node metastasis, and radiotherapy. The size of a tumor plays a crucial role in determining its invasiveness. However, there is currently a dearth of relevant studies that investigate the relationship between tumor size and the occurrence of LM in ATC. Upon ATC diagnosis, patients are categorized as stage IV based on the American Joint Committee on Cancer (AJCC) TNM staging system, irrespective of tumor size, lymph node status, or distant metastasis. According to this staging system, stage IVa denotes an intrathyroidal tumor, stage IVb represents a primary tumor with extrathyroidal extension, and stage IVc signifies the presence of distant metastasis (21,22). This classification approach to some extent masks the influence of primary tumor size on the likelihood of LM. Previous research reports have revealed a correlation between cervical lymph node metastasis and the occurrence of LM, and as the number of metastatic lymph nodes increases, the risk of LM gradually rises (23). Our study demonstrates that ATC patients with concurrent LM have a particularly poor prognosis, emphasizing the critical importance of appropriate surgical resection and radiation therapy. Subsequently, we created an innovative diagnostic nomogram utilizing the four independent predictive factors, which underwent rigorous validation through calibration curves, ROC curves, and DCA. The outstanding performance of this nomogram signifies its potential to advance the current landscape of risk assessment and bolster the precision of personalized clinical decision-making.

Furthermore, our multivariate Cox analysis results revealed that patients with a tumor size >6 cm and those who did not undergo surgery, chemotherapy, or radiation therapy had a significantly worse prognosis. The results of this study demonstrated that patients who underwent surgical resection had significantly higher OS compared to those who did not undergo surgery. The debate regarding the benefit of surgical tumor resection in prolonging life expectancy has been ongoing, as surgery, while undoubtedly important, is far from sufficient in achieving long-term survival goals for patients (24-26). The comprehensive treatment approach combining surgery with radiation and chemotherapy has been shown to improve treatment efficacy and extend the survival of patients to some extent (27,28). These findings are consistent with the results of our study. It is noteworthy that we have developed a novel prognostic nomogram to predict the prognosis of ATC patients with concurrent LM. By incorporating the prognostic factors identified in this study, healthcare professionals can more effectively assess the prognosis and provide clinical guidance for ATC patients with LM.

In recent years, molecular targeted therapy has emerged as a new approach in the treatment of ATC, providing a new perspective for its management. The effectiveness of the combination therapy of the *BRAF* gene inhibitor, dabrafenib, and the MEK inhibitor, trametinib, in treating *BRAF* V600E-positive ATC patients has been confirmed in clinical trials (29). The 2021 National Comprehensive Cancer Network Clinical Practice Guidelines for Thyroid Cancer recommend the combination of dabrafenib and trametinib as the preferred treatment for *BRAF* V600E-positive ATC patients (30). Patients with a tumor mutation

burden (TMB) of ≥10 mut/Mb may be considered for immunotherapy (31). The immune checkpoint inhibitor pembrolizumab has been employed in the treatment of high TMB thyroid cancer and can serve as the preferred approach for patients with an overexpression of programmed cell death protein 1 (PD-1) in ATC (32,33).

However, we acknowledge that there are certain limitations in our study that should be recognized. Firstly, the data for this study were obtained from a retrospective analysis of the SEER database, which may introduce selection bias (34). Secondly, obtaining additional relevant information, such as patients' cancer family history and detailed information on chemotherapy and radiation therapy, was challenging due to the limitations of the available data in the SEER database. Thirdly, although our study had a larger sample size compared to previous studies, the extremely low incidence rate of ATC resulted in a relatively small number of patients, which may have reduced the overall research value. Finally, our nomogram was constructed using the training set and validated using the validation set within our study. However, it is important to acknowledge that we did not include publicly available ATC data from other databases, which could introduce inherent bias into our findings.

Conclusions

In summary, our study employed univariate and multivariate logistic regression analyses to identify the risk factors associated with LM in ATC. Additionally, we conducted univariate and multivariate Cox regression analyses to determine the prognostic factors for ATC patients with LM. Based on these findings, we developed two nomograms that provide valuable guidance for clinical decision-making.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1195/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1195/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1195/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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