Establishment and Validation of a Risk Prediction Model for Early Postoperative Distant Metastasis in Patients With Medullary Thyroid Carcinoma

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AIM: This study aimed to investigate risk factors for early postoperative distant metastasis in patients with medullary thyroid carcinoma (MTC) and to establish a risk prediction model.

METHODS: A total of 263 patients diagnosed with MTC after initial surgery at Zhejiang Cancer Hospital between March 2015 and August 2023 were included. The patients were divided into metastasis group (n = 75) and non-metastasis group (n = 188) based on the presence of distant tumor metastasis at 3 months postoperatively. Clinical data, including demographic information, laboratory results, and ultrasound findings, were collected for both groups. The collected data were then randomly assigned into a training set (n = 187) and a validation set (n = 76) at a ratio of 7:3. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for early postoperative distant metastasis. Also, the stepwise backward method was used to determine the predictors of early postoperative distant metastasis, which were utilized for developing a nomogram. Receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) curves were adopted to evaluate the performance and predictive value of the model developed.

RESULTS: Multivariate logistic regression analysis revealed that preoperative calcitonin levels and dissection approach were independent factors associated with postoperative distant metastasis. Tumor diameter and number of lesions also showed trends associated with distant metastasis and were therefore included in the predictive model. The final predictors we used to construct the model were age, preoperative carcinoembryonic antigen (CEA), preoperative calcitonin, tumor diameter, number of lesions, and lymph node dissection method. The model demonstrated superior predictive performance, with an area under the curve (AUC) of 0.823 for the training set and 0.763 for the validation set. Calibration curves confirmed good agreement between predicted and observed probabilities. Results from DCA further supported the model's ability to effectively identify individuals at high risk of postoperative distant metastasis on both training and validation sets.

CONCLUSIONS: Incorporating readily available clinical variables, the risk prediction model for early postoperative distant metastasis in MTC demonstrated robust discriminatory ability and calibration. Further large-scale prospective studies with external validation are warranted to evaluate the clinical applicability and utility of this model in surgical decision-making.

Keywords: medullary thyroid carcinoma; distant metastasis; risk factors; decision curve analysis; prediction model

Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor arising from parafollicular C cells in the thyroid gland, accounting for 2–4% of all thyroid cancers. Despite its rarity, MTC contributes to 13.4% of thyroid cancer-related deaths [1]. MTC is a highly aggressive malignancy characterized by poor differentiation, early metastatic potential, lack of iodine uptake, and resistance to radiotherapy and chemotherapy [2,3]. Moreover, the malignant proliferation of C cells leads to increased secretion of various bioactive substances, such as calcitonin and carcinoembryonic antigen (CEA) [4]. Although MTC is less prevalent in China, there has been an upward trend in recent years. Furthermore, due to the malignant nature of MTC, the disease burden remains substantial [5].

Currently, surgery is recognized as the most effective treatment approach for MTS management [6]. However, even with reasonable follow-up and postoperative risk assessment for distant metastasis, a subset of MTC patients is at risk of distant metastases that are often overlooked, leading to poor prognosis [7,8]. Therefore, we propose that stratification of postoperative distant metastasis risk based on preoperative information can facilitate more precise surgical planning and improve patient outcomes.

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At present, both calcitonin and CEA are the most potent markers for diagnosing and monitoring distant metastasis in MTC patients postoperatively. However, neither of them can accurately predict patient prognosis when used alone [9]. It has been reported that the preoperative levels of calcitonin are affected by several factors, such as tumor diameter and lymph node involvement, determining the time required for serum calcitonin to return to normal in MTC patients postoperatively [10–12]. Meanwhile, the calcitonin doubling rate cannot provide a timely assessment of a patient's metastatic risk, potentially leading to treatment delays [13]. Furthermore, given that the association of elevated CEA levels with other tumors [14], CEA is less sensitive and specific than calcitonin in predicting distant metastasis.

Therefore, some scholars have investigated the risk of distant metastasis following MTC surgery. Previous prediction models for distant metastasis risk in MTC were all constructed using the SEER database, with an emphasis on intraoperative and postoperative indicators, such as the number of metastatic lymph nodes dissected and the extent of surgical resection [8,12]. Given the heterogeneity in genetic characteristics of MTC as well as the genetic and epigenetic differences among different ethnic groups, the performance of these SEER-based risk prediction models in the Chinese population requires further validation. This study aims to establish a risk prediction model for early postoperative distant metastasis in patients with MTC based on preoperative indicators in Chinese patients, to enable preoperative assessment of the early distant metastasis risk in MTC patients. The risk prediction model may contribute to informing the selection of appropriate surgical approaches and reducing repeated surgery due to postoperative distant metastasis in patients with MTC.

Methods

Study Population and Selection Criteria

This retrospective study included 263 patients diagnosed with MTC following initial surgery at Zhejiang Cancer Hospital between March 2015 and August 2023. We used ultrasonography for initial staging of tumors; enhanced CT was adopted then to assess the local invasion and detection of distant metastasis in MTC. The inclusion criteria are as follows: (1) patients who were diagnosed with MTC based on postoperative pathological confirmation; (2) patients who were newly diagnosed and underwent initial surgery at our hospital without receiving adjuvant radiotherapy or chemotherapy before surgery; and (3) patients who underwent at least a central neck lymph node dissection or a unilateral lateral neck lymph node dissection. Patients who did not undergo surgery for any reason or those with a medical history of malignant tumors were excluded from the present study. By applying the predefined inclusion and exclusion criteria, a total of 263 patients were enrolled and randomly divided into a training set and an internal validation set at a 7:3 ratio. The patients were divided into metastasis group (n = 75) and non-metastasis group (n = 188) based on the presence of distant tumor metastasis at 3 months postoperatively. This study adhered to the guiding principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Zhejiang Cancer Hospital (Ethics Approval No.: IRB-2024-802(IIT)). Written informed consent was obtained from every participant.

Outcome Measures

The early distant metastasis was defined as distant metastasis that occurred within 3 months postoperatively, as documented in the hospital medical records.

Data Collection

The indicators collected in this study include: (1) demographic information (including age and gender); (2) laboratory results, including preoperative calcitonin (pre-calcitonin), preoperative carcinoembryonic antigen (pre-CEA), preoperative thyroid-stimulating hormone (pre-TSH); (3) preoperative ultrasound findings, such as elasticity score, Color Doppler Flow Imaging (CDFI) score, tumor diameter, clarity of tumor margins, and number of lesions (single or multiple); (4) preoperative tumor, node and metastasis (TNM) staging; (5) preoperative surgery method (unilateral or bilateral); (6) lymph node dissection method (central or lateral neck dissection); (7) postoperative distant metastasis status (yes or no).

Management of Missing Values

For critical variables (such as maximum thyroid diameter, elasticity score, and pre-CEA), patients with multiple missing critical variables were excluded from the analysis. However, this approach may reduce sample size and introduce bias. For non-critical variables with an overall missing rate of no greater than 15%, multiple imputation methods were employed. This may affect the variance and the significance of the results.

Statistical Analysis

Statistical analysis was performed using R software (version 4.5.1, Posit Software, PBC, Boston, MA, USA). The dataset was split into training and validation sets using the "caret" package. Normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables conforming to a normal distribution are expressed as mean ± standard deviation (SD), whereas non-normally distributed data are presented as median (interquartile range, IQR). Categorical data are presented as counts and percentages. Univariate logistic regression was performed for all factors analyzed. Variables with clinical relevance or previously reported associations with distant metastasis were also included in the model, regardless of their statistical significance in univariate analysis. Variables that were included in the final model were adjusted according to their

contribution to distant metastasis in order to enhance the clinical interpretability and robustness of the model. The backward stepwise method was used to identify the predictors, which were then used to construct a nomogram. Discrimination, calibration, and clinical utility of the model were assessed using area under the curve (AUC), calibration plots, and decision curve analysis (DCA), respectively.

Results

Characteristics of Participants

There are significant differences between the metastasis group and the non-metastasis group in pre-calcitonin ($p < 0.01$), pre-CEA ($p < 0.01$), dissection method ($p < 0.01$), and N staging ($p < 0.01$; Table 1).

Variable Selection

The data were randomly divided into a training set (187 cases) and a validation set (76 cases) at a 7:3 ratio. The training set included 51 patients with distant metastasis, while the validation set contained 24 patients with distant metastasis. There are significant differences between the training and validation sets in M staging and surgery methods used (all $p < 0.05$, as shown in Table 2).

For the training set, univariate analysis revealed significant differences between the metastasis group and the non-metastasis group in the pre-calcitonin level, pre-CEA, N staging, and lymph node dissection method used (all $p < 0.05$, as shown in Table 3).

Guided by statistical screening and clinical relevance, the risk prediction model incorporated six variables, namely age, pre-calcitonin, pre-CEA, tumor diameter, number of lesions, and dissection method (Table 4).

Furthermore, collinearity diagnostics were performed to assess potential multicollinearity among predictors in the regression model. The analysis revealed no significant correlations (variance inflation factor (VIF) <5), indicating that the included variables were unaffected by multicollinearity. During model construction, N-staging was initially included in the multivariate analysis but was not retained in the final model following backward logistic regression. This indicates that, after adjusting for other covariates, it did not provide independent predictive value.

Development and Validation of the Risk Prediction Model

A predictive model was constructed using the identified predictors, such as age, pre-calcitonin, pre-CEA, tumor diameter, number of lesions, and dissection method, to predict the probability of distant metastasis in patients with MTC after surgery. Fig. 1 shows the nomogram established based on the risk prediction model. The AUCs for the training and validation sets were 0.823 (Fig. 2A) and 0.763 (Fig. 2B), respectively, indicating the robust discriminatory power and generalization ability of the model.

As shown in the calibration curve, the predicted and observed values of the model demonstrated good agreement in both the training (Fig. 3A) and validation sets (Fig. 3B), indicating satisfactory model calibration. Decision curve analysis (DCA) demonstrated that, compared with the default strategy, the model provides superior clinical benefit by yielding higher net benefit within a threshold probability range of 37.5% to 87.5%, suggesting its utility in guiding clinical decision-making (training set in Fig. 4A; validation set in Fig. 4B).

Discussion

Patients with MTC have a higher mortality rate and a poorer prognosis compared to those with differentiated thyroid carcinoma [1]. The 10-year survival rate for patients with MTC treated by surgical resection is approximately 96%, accompanied by a high risk of distant metastasis reaching up to 20% [15]. Once distant metastasis develops, the 10-year survival rate declines sharply to 40%. Furthermore, since MTC tumor cells cannot take up iodine and are insensitive to thyroid-stimulating hormone (TSH), both radioactive iodine therapy and TSH suppression therapy are ineffective for MTC. Therefore, surgery remains one of the few curative treatment options for MTC patients. It is noteworthy that the prognosis of MTC largely depends on the extent of the initial surgical removal of all detectable tumor tissues [16].

Currently, the risk of distant metastasis in MTC is primarily assessed postoperatively to facilitate the development of follow-up plans. Prognosis of patients with MTC is mainly associated with tumor stage at diagnosis and the extent of surgical resection [17]. Postoperative monitoring and follow-up commonly rely on imaging examinations (such as ultrasound and chest computed tomography [CT]), as well as CEA and calcitonin levels and their doubling time, to enable prompt detection of metastasis [18]. However, due to the long half-life of calcitonin, the predictive value of calcitonin detected within 3 months postoperatively for the risk of distant metastasis is limited, particularly in patients with hepatic or renal dysfunction or those with elevated preoperative calcitonin [13]. Current guidelines recommend using calcitonin and CEA as well as their doubling time as independent risk factors during risk assessment of distant metastasis in MTC [19], but predictive outcomes based merely on postoperative CEA or calcitonin monitoring are hardly satisfactory [8].

The risk prediction model constructed in this study integrates a range of parameters and variables for estimating distant metastasis risk, such as patient demographics, laboratory results, and surgical approach used. The model enables early identification of patients at higher risk of postoperative distant metastasis by estimating the risk during the preoperative period. Therefore, the model can guide decision-making in surgery (such as the need for prophylactic lateral neck dissection). Also, our model demonstrated favorable predictive performance in the validation dataset. For patients who are identified as having an in-

Table 1. Comparison of baseline and clinical characteristics between the metastasis and non-metastasis groups.

	Metastasis group (n = 75)	Non-metastasis group (n = 188)	p-value
Age (years)	48.00 (40.50, 59.50)	53.50 (45.00, 61.25)	0.05
Gender			0.81
Male	34 (45.3%)	90 (47.9%)	
Female	41 (54.7%)	98 (52.1%)	
Pre-calcitonin (pg/mL)	220.50 (60.02, 683.20)	902.00 (205.25, 2000.00)	<0.01
Pre-CEA (ng/mL)	8.71 (2.79, 25.40)	25.38 (5.20, 69.88)	<0.01
Pre-TSH (μlU/mL)	1.35 (0.85, 2.23)	1.26 (0.55, 2.10)	0.54
Elasticity score			0.13
1	7 (9.33%)	30 (16.0%)	
2	21 (28.0%)	52 (27.7%)	
3	31 (41.3%)	81 (43.1%)	
4	14 (18.7%)	25 (13.3%)	
5	2 (2.67%)	0 (0.00%)	
CDFI score			0.17
0	38 (50.7%)	94 (50.0%)	
1	12 (16.0%)	28 (14.9%)	
2	12 (16.0%)	26 (13.8%)	
3	11 (14.7%)	40 (21.3%)	
4	2 (2.67%)	0 (0.00%)	
Tumor margin			0.28
Clear	21 (28.0%)	67 (35.6%)	
Partially clear	19 (25.3%)	33 (17.6%)	
Unclear	35 (46.7%)	88 (46.8%)	
Tumor diameter (mm)	15.00 (9.50, 25.00)	16.00 (10.00, 27.00)	0.40
Number of lesions			0.14
Single	34 (45.3%)	65 (34.6%)	
Multiple	41 (54.7%)	123 (65.4%)	
Lymph node dissection method			<0.01
Lateral neck dissection	24 (32.0%)	134 (71.3%)	
Central dissection	51 (68.0%)	54 (28.7%)	
T staging			0.08
x	23 (30.7%)	84 (44.7%)	
1	37 (49.3%)	59 (31.4%)	
2	9 (12.0%)	25 (13.3%)	
3	3 (4.00%)	6 (3.19%)	
4	3 (4.00%)	14 (7.45%)	
M staging			0.78
0	70 (93.3%)	177 (94.1%)	
1	5 (6.67%)	11 (5.85%)	
N staging			<0.01
x	37 (49.3%)	49 (26.1%)	
1	37 (49.3%)	139 (73.9%)	
2	1 (1.33%)	0 (0.00%)	
Surgery method			0.12
Unilateral	34 (45.3%)	64 (34.0%)	
Bilateral	41 (54.7%)	124 (66.0%)	

Note: 'x' indicates situations where the primary tumor (T) or regional lymph node (N) status cannot be assessed ('Tx' and 'Nx' in TNM staging), respectively.

Abbreviations: Pre-calcitonin, preoperative calcitonin; Pre-CEA, preoperative carcinoembryonic antigen; Pre-TSH, preoperative thyroid-stimulating hormone; CDFI, Color Doppler Flow Imaging; T, tumor; N, node; M, metastasis.

Table 2. Comparison of baseline and clinical characteristics between the training and validation sets.

	Validation set (n =76)	Training set (n = 187)	p-value
Age (years)	53.5 (45.8, 61.0)	53.0 (43.0, 61.0)	0.43
Gender			0.53
Male	33 (43.4%)	91 (48.7%)	
Female	43 (56.6%)	96 (51.3%)	
Pre-calcitonin (pg/mL)	898.1 (175.3, 1761.1)	616.0 (138.8, 2000.0)	0.85
Pre-CEA (ng/mL)	18.3 (4.6, 74.7)	18.3 (4.2, 54.3)	0.53
Pre-TSH (μlU/mL)	1.2 (0.5, 2.0)	1.3 (0.7, 2.2)	0.89
Elasticity score			0.69
1	9 (11.8%)	28 (15.0%)	
2	21 (27.6%)	52 (27.8%)	
3	31 (40.8%)	81 (43.3%)	
4	14 (18.4%)	25 (13.4%)	
5	1 (1.3%)	1 (0.5%)	
CDFI score			0.41
0	38 (50.0%)	94 (50.3%)	
1	9 (11.8%)	31 (16.6%)	
2	15 (19.7%)	23 (12.3%)	
3	13 (17.1%)	38 (20.3%)	
4	1 (1.3%)	1 (0.5%)	
Tumor margin			0.06
Clear	33 (43.4%)	55 (29.4%)	
Partially clear	10 (13.2%)	42 (22.5%)	
Unclear	33 (43.4%)	90 (48.1%)	
Tumor diameter (mm)	17.50 (11.00, 27.25)	15.00 (10.00, 26.00)	0.31
Number of lesions			0.98
Single	28 (36.8%)	71 (38.0%)	
Multiple	48 (63.2%)	116 (62.0%)	
Lymph node dissection method			0.25
Lateral neck dissection	41 (53.9%)	117 (62.6%)	
Central dissection	35 (46.1%)	70 (37.4%)	
T staging			0.58
x	35 (46.1%)	72 (38.5%)	
1	24 (31.6%)	72 (38.5%)	
2	9 (11.8%)	25 (13.4%)	
3	4 (5.3%)	5 (2.7%)	
4	4 (5.3%)	13 (7.0%)	
M staging			<0.01
0	66 (86.8%)	181 (96.8%)	
1	10 (13.2%)	6 (3.21%)	
N staging			0.84
x	26 (34.2%)	60 (32.1%)	
1	50 (65.8%)	126 (67.4%)	
2	0 (0.0%)	1 (0.5%)	
Surgery method			0.01
Unilateral	18 (23.7%)	80 (42.8%)	
Bilateral	58 (76.3%)	107 (57.2%)	
Distant metastasis			0.58
Yes	24 (31.6%)	51 (27.3%)	
No	52 (68.4%)	136 (72.7%)	

Note: 'x' indicates situations where the primary tumor (T) or regional lymph node (N) status cannot be assessed ('Tx' and 'Nx' in TNM staging), respectively.

Table 3. Comparison of baseline and clinical characteristics between the metastasis and non-metastasis groups within the training set.

	Metastasis group (n = 51)	Non-metastasis group (n = 136)	p-value
Gender			0.67
Male	23 (45.1)	68 (50.0)	
Female	28 (54.9)	68 (50.0)	
Age (years)	50.00 (39.00, 61.50)	53.00 (44.00, 61.00)	0.29
Pre-calcitonin (pg/mL)	264.00 (67.65, 658.35)	827.85 (174.50, 2000.00)	<0.01
Pre-CEA (ng/mL)	8.71 (3.05, 24.27)	25.37 (4.84, 61.32)	<0.01
Pre-TSH (μlU/mL)	1.35 (0.94, 2.38)	1.30 (0.59, 2.10)	0.43
Elasticity score			0.49
1	6 (11.8)	22 (16.2)	
2	14 (27.5)	38 (27.9)	
3	22 (43.1)	59 (43.4)	
4	8 (15.7)	17 (12.5)	
5	1 (2.0)	0 (0.0)	
CDFI score			
0	25 (49.0)	69 (50.7)	0.34
1	11 (21.6)	20 (14.7)	
2	6 (11.8)	17 (12.5)	
3	8 (15.7)	30 (22.1)	
4	1 (2.0)	0 (0.0)	
Tumor diameter (mm)	14.00 (9.00, 24.00)	15.00 (10.00, 27.00)	0.22
Tumor margin			
Clear	12 (23.5)	43 (31.6)	0.45
Partially clear	14 (27.5)	28 (20.6)	
Unclear	25 (49.0)	65 (47.8)	
Number of lesions			
Single	24 (47.1)	47 (34.6)	0.16
Multiple	27 (52.9)	89 (65.4)	
T staging			
x	14 (27.5)	58 (42.6)	0.08
1	28 (54.9)	44 (32.4)	
2	6 (11.8)	19 (14.0)	
3	1 (2.0)	4 (2.9)	
4	2 (3.9)	11 (8.1)	
M staging			
0	50 (98.0)	131 (96.3)	0.90
1	1 (2.0)	5 (3.7)	
N staging			
x	23 (45.1)	37 (27.2)	0.01
1	27 (52.9)	99 (72.8)	
2	1 (2.0)	0 (0.0)	
Surgery method			
Unilateral	26 (51.0)	54 (39.7)	0.22
Bilateral	25 (49.0)	82 (60.3)	
Lymph node dissection method			
Lateral neck dissection	19 (37.3)	98 (72.1)	<0.01
Central dissection	32 (62.7)	38 (27.9)	

Note: 'x' indicates situations where the primary tumor (T) or regional lymph node (N) status cannot be assessed ('Tx' and 'Nx' in TNM staging), respectively.

creased risk of postoperative distant metastasis, the model facilitates meticulous formulation of a personalized surgical plan, including consideration of prophylactic lateral neck lymph node dissection. Due to limited data availability, this

Table 4. Logistic regression analysis of selected predictors of distant metastasis in the training set.

	β	Standard error	Wald	OR (95% CI)	p
Age (years)	0.0169	0.0118	1.43	1.02 (0.99, 1.04)	0.15
Pre-calcitonin (pg/mL)	0.0007	0.0003	2.64	1.00 (1.00, 1.00)	0.01
Pre-CEA (ng/mL)	0.0002	0.0003	0.61	1.00 (1.00, 1.00)	0.54
Tumor diameter (mm)	–0.0244	0.0141	–1.73	0.98 (0.95, 1.00)	0.08
Number of lesions					
Single	0			1	
Multiple	0.5911	0.3238	1.83	1.81 (0.96, 3.43)	0.07
Lymph node dissection method					
Lateral neck dissection	0			1	
Central dissection	–1.3803	0.3275	–4.21	0.25 (0.13, 0.47)	<0.01

Abbreviations: CI, Confidence interval; OR, Odds ratio.

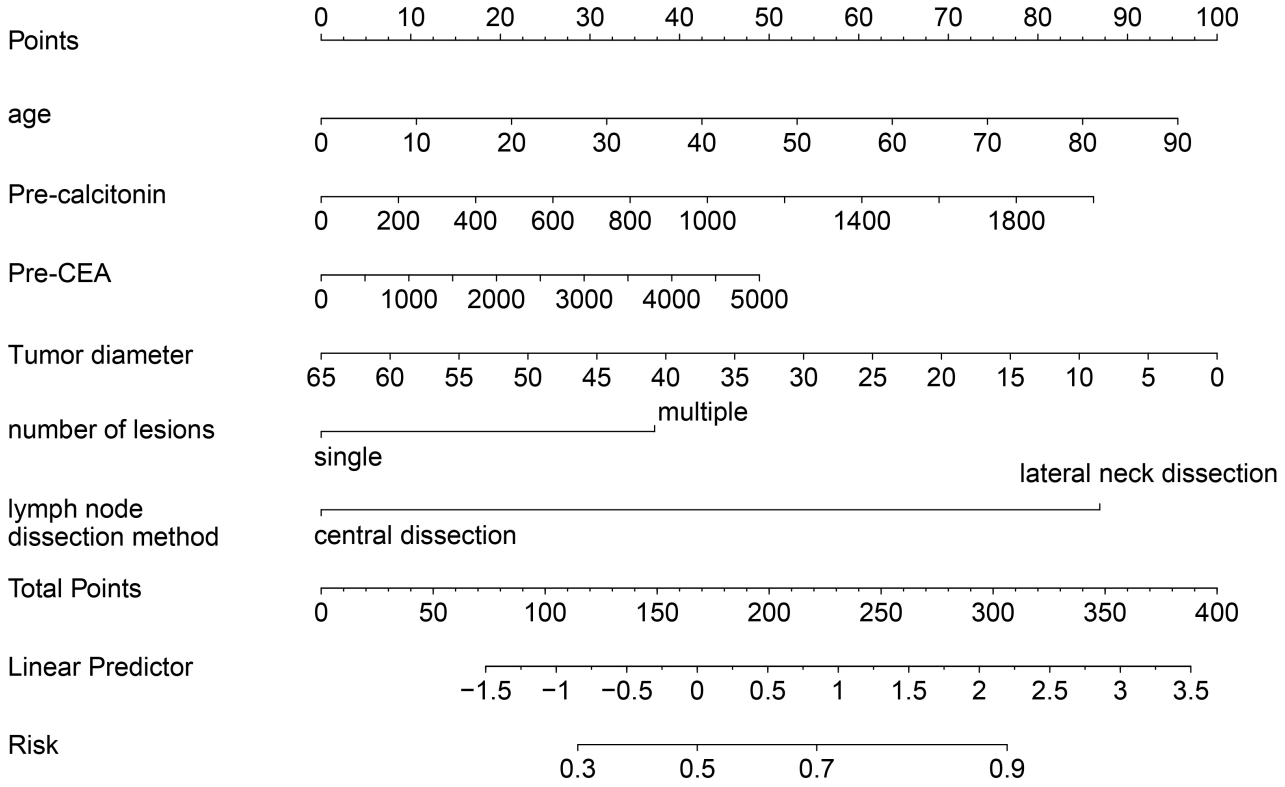

Fig. 1. Nomogram for predicting the risk of postoperative distant metastasis in medullary thyroid carcinoma.

study examined only the individual impact of central neck lymph node dissection and lateral neck lymph node dissection on patient prognosis. Our results revealed that central neck lymph node dissection holds more pronounced beneficial effect on patient prognosis.

Certain variables, such as age and CEA, that did not achieve statistical significance in the univariate analysis were nevertheless incorporated into the final model given their established clinical relevance in previous studies [12,19,20] and their potential synergistic effects within the predictive model. Furthermore, calcitonin and CEA, along with their doubling time, have been recommended as independent risk factors for assessing distant metastasis risk in MTC [19]. This underscores that selecting variables solely on the basis of statistical significance may lead to model underfitting or reduced generalization performance, whereas incorporating clinically meaningful predictors can enhance the model's overall performance. The calibration curves of the model constructed in this study uncovered good agreement between predicted and observed values in both the training and validation sets, indicating that the model possesses strong discriminatory capability.

All variables included in the final model are clinically relevant to distant metastasis in the context of MTC. Calcitonin is a specific biomarker for MTC, with higher levels typically indicating a greater cancer burden and a higher degree of tumor aggressiveness. Elevated preoperative calcitonin has been demonstrated to correlate strongly with lymph

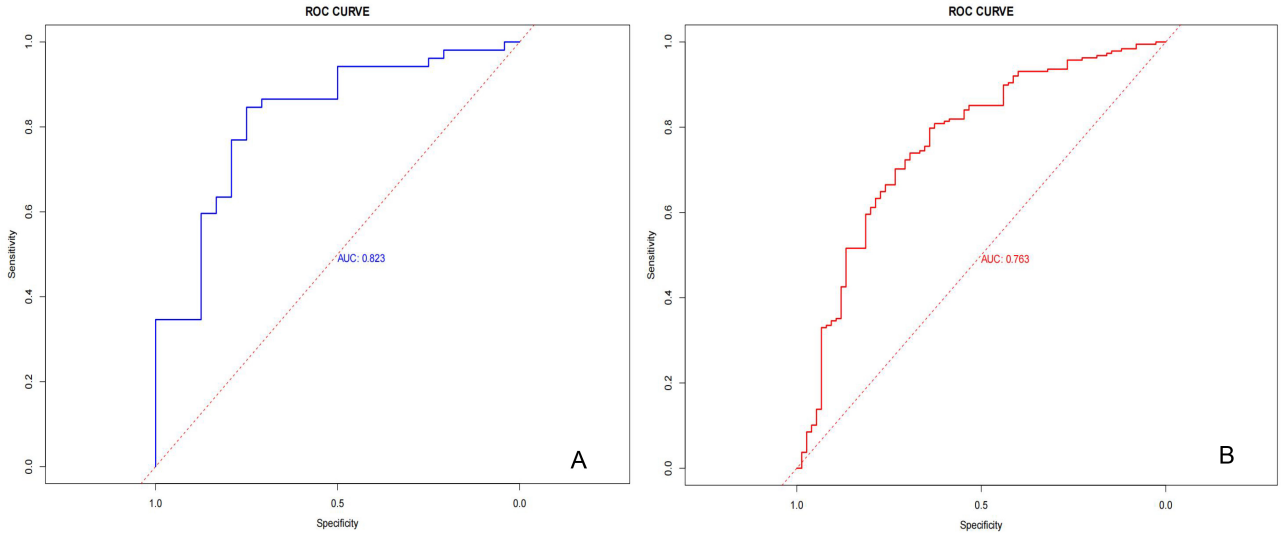

Fig. 2. ROC curves of the predictive model. (A) ROC curve for the training set. (B) ROC curve for the validation set. ROC, receiver operating characteristic; AUC, area under the curve.

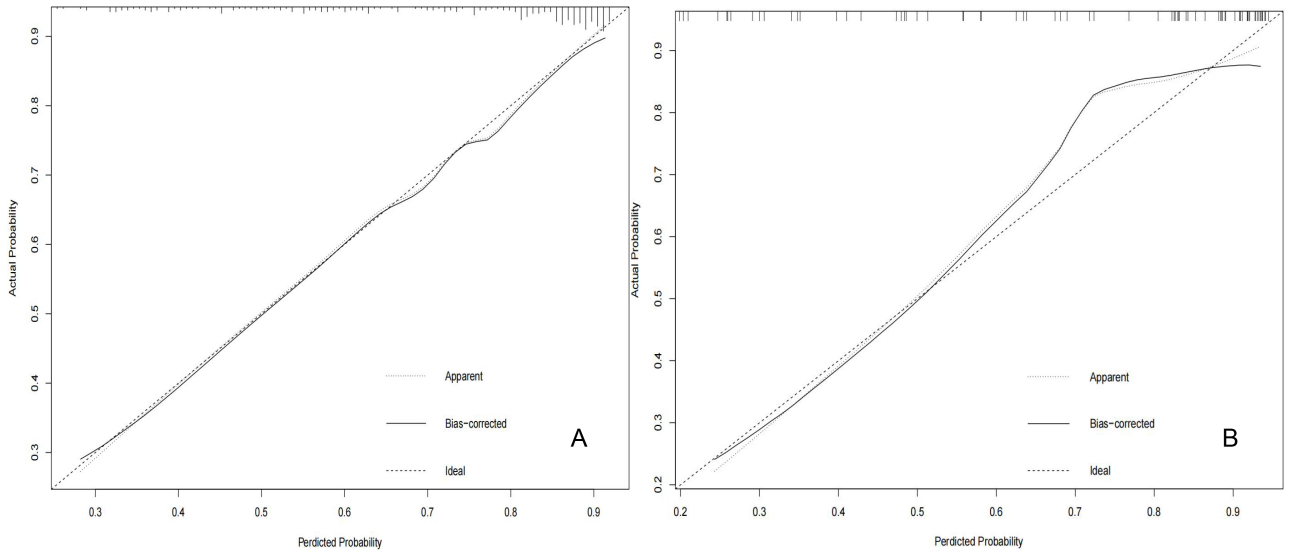

Fig. 3. Calibration curves of the predictive model. (A) Calibration curve for the training set. (B) Calibration curve for the validation set.

node metastasis and distant metastasis, because calcitonin production directly reflects the secretory activity and malignancy of the cancer originating from C cells [21–23]. Also, pre-calcitonin showed a strong association with lymph node metastasis [24]. The presence of central and lateral neck lymph node metastases typically signals an increased risk of distant disease. Metastases to lateral neck lymph node may reflect a more severe disease state as well as a higher risk of distant metastasis [25,26]. Taken together, the inclusion of these variables as predictors in the model is justifiable based on these published results.

Larger tumor diameter is associated with higher levels of invasiveness and metastatic risk [23,24,27]. In this study, patients with larger tumor diameters experienced less metastasis risk, probably due to higher-intensity treatments received to tackle the aggressiveness and invasiveness of the larger tumor. Previous studies indicate that older age (>55 years) increases the risk of distant metastasis in patients with MTC postoperatively [12,20]; therefore, age was included in the final model as a predictor in this study. CEA is a non-specific biomarker used to characterize tumor aggressiveness, with elevated levels associated with advanced tumor status and higher-grade metastatic risk. Its combination with calcitonin further enhances the accuracy of predicting distant metastasis [28,29]. Regarding the number of lesions, the involvement of more than one location typically reflects a more extensive pattern of tumor dissemination and is associated with regional lymph node and dis-

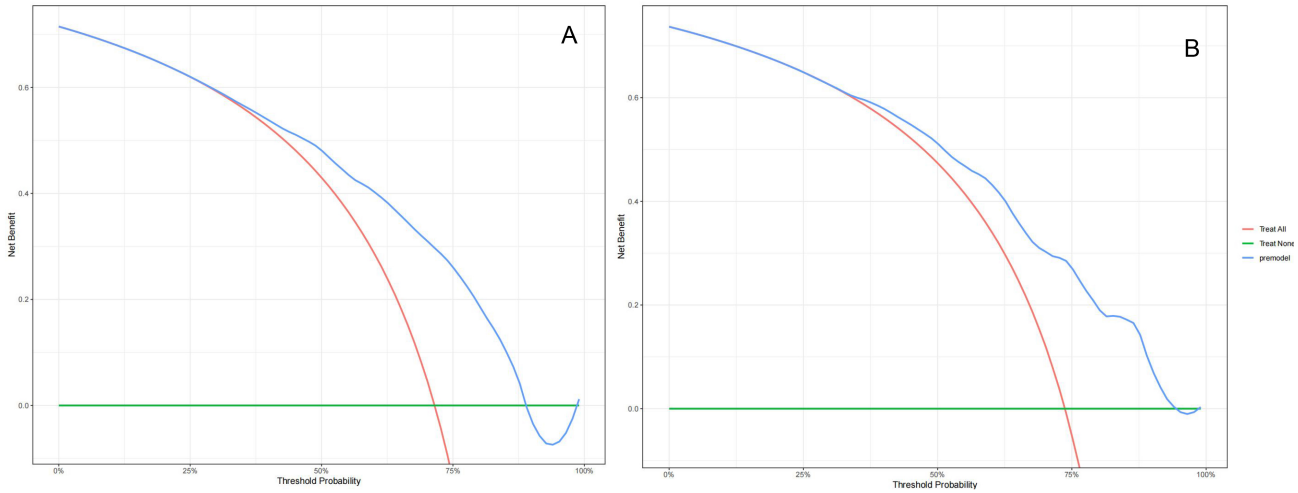

Fig. 4. DCA curves of the predictive model. (A) DCA curve for the training set. (B) DCA curve for the validation set. Abbreviation: DCA, decision curve analysis.

tant metastases. The presence of multiple lesions in patients with MTC generally indicates a more aggressive disease course [27,30].

Previous prediction models focused on the estimation of lateral lymph node metastasis or recurrence. A previous study has reported the development of a preoperative prediction model for cervical lymph node metastasis based on data from 74 patients and three variables (tumor margin, ultrasound findings of lymph node involvement, and extracapsular invasion). The model had an AUC of 0.919, but it might be attributed to overfitting due to the small sample size [26]. Another prediction model for distant metastasis in MTC was constructed using data obtained from the SEER database (2004–2015), incorporating factors such as age, T stage, N stage, and lymph node ratio. Despite a high AUC (0.894) demonstrated in the ROC analysis, the model is not applicable to Chinese people, because substantial differences remain between the Chinese and American populations in terms of genetic background, lifestyle, and environment [12]. Also, some predictors in this model cannot be collected preoperatively. Therefore, compared with the preoperative prediction model developed in other studies, our risk prediction model incorporates ultrasound-related, biochemical, and demographic variables, which are holistically representative of the MTC patients' profile, to enhance the predictive accuracy while reducing the possibility of overfitting. Our model was based on values from routine practice, which would not add additional burden to the patients. Also, it can be assessed preoperatively, thereby facilitating early diagnosis and targeted intervention.

Limitations & Future Directions

However, this study has certain limitations. First, several key variables such as gene monitoring and preoperative Fine needle aspiration (FNA) testing were excluded from the prediction model due to substantial missing data. For variables with a missing rate <15%, although multiple imputations were employed to minimize discrepancies from the actual data, some bias remains unavoidable. Furthermore, although previous studies have shown that the risk of postoperative distant metastasis increases with higher TNM staging [8], preoperative TNM staging was excluded from the final model, possibly due to bias arising from the small sample size. Ultrasound-related indicators were excluded for the following reasons: the elasticity score in our nomogram exhibited a trend completely opposite to routine clinical practice, and the CDFI score contributed only minimally to explaining the dependent variable, which may also be attributable to the small sample size of this study. The observed tumor diameter is inconsistent with the real-world values obtained in clinical settings, likely due to the small sample size of this study. Contradictions between regression coefficients for some variables in this study and clinical intuition could stem from several factors: (1) The presence of confounding variables. Tumor size is a well-established risk factor of metastasis in MTC. Nevertheless, as tumor diameter is often used to guide treatment intensity, patients harboring larger tumors typically receive more aggressive therapies, including chemotherapy, which contributes to lower long-term metastasis risk. Thus, the observed counterintuitive association between large tumor size and reduced long-term postoperative metastasis risk likely reflects the influence of confounding variables not already discovered or analyzed in the present study; (2) Potential selection bias. This study exclusively included patients who underwent successful surgical resection, excluding those with unresectable large tumors. Based on the variance inflation factor, multicollinearity remains within an acceptable range.

This study failed to differentiate the sporadic medullary cancers from familiar MTC represents. Moreover, using the "presence of metastasis within 3 months postopera-

tively" cutoff for defining early distant metastasis in the present study may fail to differentiate newly emerging distant metastases from those already present preoperatively, because preexisting metastasis could be misclassified due to failed detection during imaging studies. Also, since the data concerning dissection method was collected preoperatively, our model can only be used for preoperative risk assessment to guide surgical planning.

Notably, although no additional follow-up data were collected, it is recommended to use existing data (such as by excluding perioperative metastasis cases) for a robustness test to further verify the reliability of our model, which will be explored in future work. Also, the model uses a single random split for internal validation. Although this method can provide a preliminary assessment of model performance, it may not fully capture the variability caused by random sampling. Stratified sampling or k-fold cross-validation can more robustly evaluate the model's generalization ability. Future studies with larger multicenter cohorts are needed to further validate our findings.

The significant differences in M staging and surgery method between the training and validation sets may stem from the relatively small sample size and random variations during dataset splitting. Nevertheless, the model maintained robust predictive performance across both datasets, suggesting no substantial impairment to its generalization capability. We acknowledge that the imbalance in clinical characteristics between the training and validation sets represents a limitation of this study. Future research with larger, multicenter datasets and stratified sampling is warranted to further validate our findings.

The applicability of the risk prediction model developed in this pilot study is limited due to the small sample size used. To expand its usability, future studies should focus on constructing prediction models for hereditary and sporadic MTC. In particular, this is achievable through prospective, multicenter studies involving large samples to comprehensively analyze socio-demographic factors, laboratory findings (including pre-CEA and pre-calcitonin), as well as FNA test and genetic test results. Such analysis will aid in the establishment of extensively validated and updated models, which would find broad applicability in guiding the formulation of tailored surgical plans and improving the overall prognosis of patients with MTC.

Conclusions

In this study, we constructed a risk prediction model for early postoperative distant metastasis in MTC patients, incorporating age, preoperative calcitonin and CEA levels, tumor diameter, number of lesions, and dissection method as predictors. This model demonstrated good discriminatory power and accuracy, allowing effective identification of patients at high risk for postoperative metastasis. However, limitations such as missing data and a small sample size warrant consideration. Future studies should focus on external validation and model updating to enhance its applicability and improve patient prognoses on a broader scale.

Availability of Data and Materials

All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

YZZ and JLG designed this research program. WHZ, XLN and JBS collected and analyzed the data. YZZ and WHZ drafted the initial manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study adhered to the guiding principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Zhejiang Cancer Hospital (Ethics Approval No.: IRB-2024-802(IIT)). All participants provided written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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