Clinics in Oncology

Research Article
Published: 04 Oct, 2023

Nomogram for Predicting Lateral Lymph Node Metastasis in Medullary Thyroid Carcinoma: A Retrospective Cohort Study of Single Clinical Center

*Xu J[1#], Li R[2#], Zhang W[1#] and Wang C[1]**

[1]Department of Pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China

[2]Nankai University School of Medicine, Tianjin, China

[#]These authors contribute equally to this work

Abstract

Background: Medullary Thyroid Carcinoma (MTC) is a neuroendocrine tumor originating from parafollicular C cells of the thyroid, accounting for only 5% of all thyroid carcinomas. Lateral Lymph Nodes Metastasis (LLNM) are the most important indicator of distant metastasis and clinical outcomes. Surgery is the only curative treatment for MTC, which is recommended to remove all lesions in the neck. We aim to establish a nomogram assessing risk factors of LLNM in MTC patients, and help surgeons make preoperative therapeutic decisions.

Materials and Methods: Totally 63 patients of a single clinical center between January 2013 and December 2020 were studied. Univariate and multivariate analysis were performed to examine risk factors associated with Central lymph Node Metastasis (CNM) and LLNM. A nomogram for predicting LLNM was established.

Results: Several preoperative clinical features were found to be significantly associated with LLNM and were used to construct the model, including diameter >1.6 cm, calcitonin (CT) >658.87 pg/mL, Carcinoembryonic Antigen (CEA) >60 ng/ml. The nomogram had good discrimination with a concordance index of 0.961 (95% Confidence Interval [CI], 0.916 to 1). A decision curve analysis was made to evaluate the nomogram.

Conclusion: A nomogram was made to predict the probability of LLNM in patients presenting with MTC, which would help surgeons make appropriate therapeutic decisions.

Keywords: Nomogram; Lateral lymph node metastasis; Medullary thyroid carcinoma; Risk factors

OPEN ACCESS

Correspondence:
Chaofu Wang, Department of Pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai200025, China, Tel: +021-64370045

Received Date: *14 Sep 2023*
Accepted Date: *28 Sep 2023*
Published Date: *04 Oct 2023*

Citation:
Xu J, Li R, Zhang W, Wang C. Nomogram for Predicting Lateral Lymph Node Metastasis in Medullary Thyroid Carcinoma: A Retrospective Cohort Study of Single Clinical Center. Clin Oncol. 2023; 8: 2019.

ISSN: 2474-1663

Introduction

Medullary Thyroid Carcinoma (MTC) is a neuroendocrine tumor originating from parafollicular C cells of the thyroid, with sporadic MTC accounting for 75% [1]. Although the incidence of MTC is much lower than Differentiated Thyroid Carcinoma (DTC), accounting for only 5% of all thyroid carcinomas, MTC is considered to have higher mortality than DTC and represents 13% of deaths caused by thyroid carcinoma [2]. Currently, the only curative treatment for MTC is surgery. Total thyroidectomy and central Compartment Lymph Node Dissection (CLND) are recommended by international guidelines [3,4], but the necessity for cN0 MTC patients to undergo ipsilateral or bilateral cervical dissection is still controversial. Therefore, patients should be examined carefully before surgery to assess the condition of Central Lymph Node Metastasis (CNM) and Lateral Lymph Nodes Metastasis (LLNM), which is the most important indicator of distant metastasis and clinical outcomes.

Calcitonin (CT) is a polypeptide hormone composed of 32 amino acids synthesized and secreted by parafollicular C cells. As previous studies shown [5-7], serum calcitonin is the most sensitive and specific tumor marker of MTC and is widely used in preoperative diagnosis and postoperative monitoring of MTC. Carcinoembryonic Antigen (CEA) is another tumor marker of MTC, but the specificity is not stronger than that of CT. In the progress of tumor dedifferentiation, the production and secretion of CT will be relatively reduced; however, serum CEA has a tendency to increase [8]. Therefore, we believe that the combined detection of CT and CEA plays an important role in the

early detection and risk stratification of MTC patients.

In this study, we examined the clinical features of patients with MTC in order to better reveal the correlation between the preoperative clinical feature with CNM and LLNM. Our comprehensive nomogram may provide new aspects of selecting the appropriate therapeutic strategy for patients with MTC.

Material and Methods

Patients

We retrospectively studied a total of 87 consecutive patients who underwent thyroid surgery for the treatment of MTC at Shanghai Ruijin Hospital between January 2013 and December 2020. The inclusion criteria for our study were as follows: 1) an obvious pathologic diagnosis of MTC; 2) primary cases without history of other thyroid tumors; 3) accepted radical surgery treatment without tumor residual; 4) without any anti-cancer therapies to reduce tumor burden before surgery, such as radiotherapy, iodine-131 therapy, targeted therapy, chemotherapy and radioisotope treatment; 5) the clinical data were complete. After exclusion, this study enrolled 63 patients pathologically diagnosed with MTC. Forty-seven patients (January 2013 to December 2019) were used to make the original model, while 16 patients (January 2020 to December 2020) were used for external validation.

Preoperative and postoperative examination

The preoperative and postoperative clinicopathological features were retrospectively studied and included the following variables: Age, sex, primary tumor size, multifocality, capsular invasion, CT, CEA, Thyroglobulin (TG), Thyroid Stimulating Hormone (TSH); Antibodies against Thyroglobulin (TGAb), Antibodies against Thyroid Peroxidase (TPOAb), the condition of CNM and LLNM. Moreover, we collected Ultrasonography (US) and US-guided Fine-Needle Aspiration (FNA) information of patients. Due to the limitation of detection, RET gene was not detected in every patient. The data related to RET gene were not collected in this paper.

Procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Shanghai Ruijin Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics 20.0 software (SPSS Inc, Chicago, IL, USA). The Chi-square test was used for nominal variables. The continuous variable was presented as mean ± SD, and Mann–Whitney test was used for these variables. Multivariate analysis was performed using binary logistic regression to determine the predictive factor for CNM and LLNM. P-values were two-tailed, and $P<0.05$ was accepted as statistically significant. R software (ver. 4.2.1, R Development Core Team) was used to construct a risk prediction model-Nomogram. The discrimination and consensus degree of our predictive model were tested through the Receiver Operating Characteristic (ROC) curve, the calibration curve, the area under the ROC curve (AUC), and the Concordance index (C-index). Decision Curve Analysis (DCA) was used to evaluate the nomogram model for prediction of LLNM.

Results

Clinicopathological characteristics of patients

In total, 47 patients, including 19 males and 28 females received thyroid surgery in Shanghai Ruijin hospital were recruited into this study. Mean age was 43.31 years with a range of 13 to 71 years. Through postoperative pathological diagnosis, the mean size of diameter was 1.77 cm with a range of 0.2 cm to 6.0 cm. Twenty-eight patients (59.57%) were found to have more than one lesion in thyroid (multifocality) and 7 patients (14.89%) were diagnosed with capsular invasion. The medium of preoperative CT and CEA were 338.11 pg/mL and 13.58 ng/mL, respectively. Before surgery, all of 47 patients have undergone US examination and the scores were higher than Thyroid Imaging Reporting and Data System (TI-RADS) 4A. Fifteen patients underwent FNA and all results indicated MTC. Finally, 47 patients have accepted CLND and 19 patients have accepted Lateral compartment Lymph Node Dissection (LLND). CNM in our study occurred in 29 (61.70%) patients, and LLNM was found in 11 patients (23.40%). In central compartment, we harvested 335 lymph nodes in total, 111 (33.13%) of which were positive lymph nodes. In lateral compartment, we harvested 465 lymph nodes in total, 94 (20.22%) of which were positive lymph nodes. Mean harvested lymph node number and mean positive lymph node number were shown in Table 1. We observed no case with lymph node jumping metastasis.

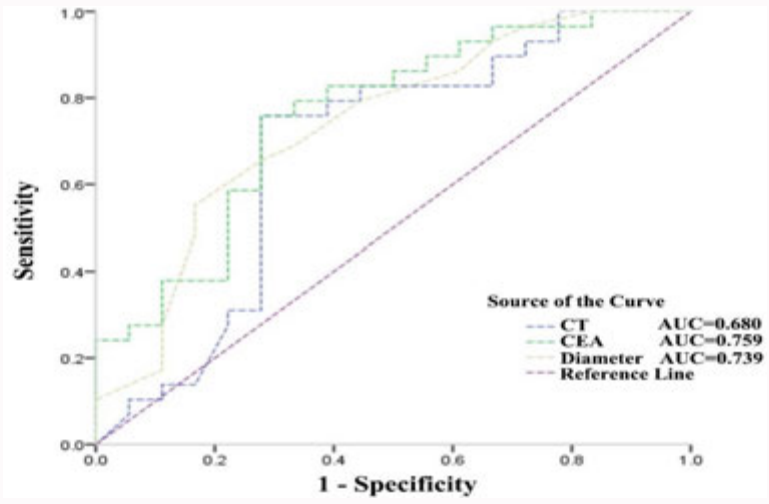

Figure 1: ROC Curves of CT, CEA, Diameter detection for CNM of medullary thyroid carcinoma patients.
CT: Calcitonin; CEA: Carcinoembryonic Antigen; CNM: Central Lymph Node Metastasis

Table 1: Demographics and clinical characteristics of patients.

Variable	Value
Number of patients	47
Age (yr)	
Mean	43.31
Sex	
Male	19 (40.42)
Female	28 (59.58)
Diameter (cm)	
Mean	1.77
Medium	1.50
CT (pg /ml)	
Mean	598.17
Medium	338.11
CEA (ng/ml)	
Mean	56.82
Medium	13.58
US	
TI-RADS 4A	23 (48.94)
TI-RADS 4B	12 (25.53)
TI-RADS 4C	8 (17.02)
TI-RADS 5	4 (8.51)
FNA	15 (31.91)
Multifocality	28 (59.57)
Capsular invasion	7 (14.89)
CLND	47 (100)
CNM	29 (61.70)
Central lymph node	
Mean harvested	7.13
Mean positive	2.36
LLND	19 (40.42)
LLNM	11 (23.40)
Lateral lymph node	
Mean harvested	24.47
Mean positive	4.94

Values are presented as number (%) unless otherwise indicated.
CT: Calcitonin; CEA: Carcinoembryonic Antigen; US: Ultrasonography; TI-RADS: Thyroid Imaging Reporting and Data System; FNA: Fine-Needle Aspiration; CLND: Central Compartment Lymph Node Dissection; CNM: Central Lymph Node Metastasis; LLND: Lateral Compartment Lymph Node Dissection; LLNM: Lateral Lymph Node Metastasis

Comparison of clinical features associated with the occurrence of CNM of MTC patients

As shown in Table 2, univariant analysis (The Chi-square test and Mann–Whitney test) indicated several clinical features predicted the occurrence of CNM of MTC patients, including sex (P=0.031), diameter (P=0.006), CT (P=0.040), CEA (P=0.003). Furthermore, we made ROC curves to evaluate the predicted value of clinical features for CNM (Figure 1). The cutoff value of CEA for predicting CNM of MTC patients was 11.23 ng/ml (Sensitivity 75.9%, Specificity 72.2%, AUC=0.759). The AUC of CT and diameter for predicting CNM of MTC patients were lower than that of CEA (AUC $_{CT}$=0.680,

Table 2: Univariate analysis showing preoperative clinical features associated with the occurrence of CNM of MTC patients.

Variables	CNM		P-value
	Positive (n=29)	Negative (n=18)	
Sex, Category, n (%)			0.031
Male	16 (55.17)	4 (22.22)	
Female	13 (44.83)	14 (77.78)	
Age, mean ± SD, y	44.03 ± 16.35	42.17 ± 14.11	0.691
Diameter, Mean ± SD, cm	2.09 ± 1.24	1.25 ± 0.94	0.006
Multifocality, Category, n (%)			0.096
Yes	20 (68.97)	8 (44.44)	
No	9 (31.03)	10 (55.56)	
Capsular invasion, Category, n (%)			0.131
Yes	7 (24.14)	1 (5.56)	
No	22 (75.86)	17 (94.44)	
Serum index			
CT, Mean ± SD, pg /ml	691.84 ± 585.11	447.24 ± 615.81	0.040
CEA, Mean ± SD, ng/ml	84.44 ± 171.55	12.33 ± 14.42	0.003
TG, Mean ± SD, ng/mL	23.43 ± 48.58	34.63 ± 68.97	0.922
TSH, Mean ± SD, μIU/mL	2.01 ± 1.19	1.67 ± 0.55	0.743
TGAb, Mean ± SD, IU/mL	0.68 ± 2.06	54.58 ± 229.81	0.818
TPOAb, Mean ± SD, IU/mL	1.42 ± 0.94	27.79 ± 101.2	0.662

CT: Calcitonin; CEA: Carcinoembryonic Antigen; TG: Thyroglobulin; TSH: Thyroid Stimulating Hormone; TGAb: Antibodies against Thyroglobulin; TPOAb: Antibodies against Thyroperoxidase; CNM: Central Lymph Node Metastasis

Table 3: Multivariate analysis of preoperative clinical features to the occurrence of CNM of MTC patients.

	OR (95%CI)	P-value
Sex (Male vs. Female**)**	1.331 (0.253-7.011)	0.736
Diameter (>1.6 *vs.* ≤ 1.6)	3.251 (0.626-16.895)	0.161
CT (>219.85 *vs.* ≤ 219.85)	4.329 (0.974-19.237)	0.054
CEA (>11.23 *vs.* ≤ 11.23)	5.119 (1.167-22.4545)	0.030

CT: Calcitonin; CEA: Carcinoembryonic Antigen; CNM: Central Lymph Node Metastasis; OR: Odds Ratio; CI: Confidence Interval

Sensitivity 75.9%, Specificity 72.2%; AUC $_{Diameter}$=0.739, Sensitivity 55.2%, Specificity 83.3%, respectively). Grouping and subsequent analysis were conducted according to cutoff value from ROC curve of CEA (11.23 ng/ml), CT (219.85 pg /ml) and Diameter (1.6 cm). Multivariate logistic regression indicated CEA >11.23 ng/mL was the significant variable associated with CNM (Table 3).

Comparison of clinical features associated with the occurrence of LLNM of MTC patients

In the univariate analysis (The Chi-square test and Mann–Whitney test), sex (p=0.019), Diameter (p=0.004), CT (p=0.003), CEA (p=0.038) and CLM (p=0.034) were associated with LLNM (Figure 2A). ROC curves were made to evaluate the predicted value of clinical features for LLNM (AUC $_{CT}$=0.801, Sensitivity 90.9%, Specificity 80.6%; AUC $_{CEA}$=0.869, Sensitivity 72.7%, Specificity 86.1%; AUC $_{diameter}$=0.854, Sensitivity 90.9%, Specificity 75.0%, respectively) (Figure 3). The cutoff value from ROC curve of Diameter and CT were 1.6 cm and 658.87 pg/ml, respectively. Besides, we observed extreme elevation of serum CEA in some patients (The normal range was 0-5 ng/ml). For further exploration, we took 12 times of the normal upper

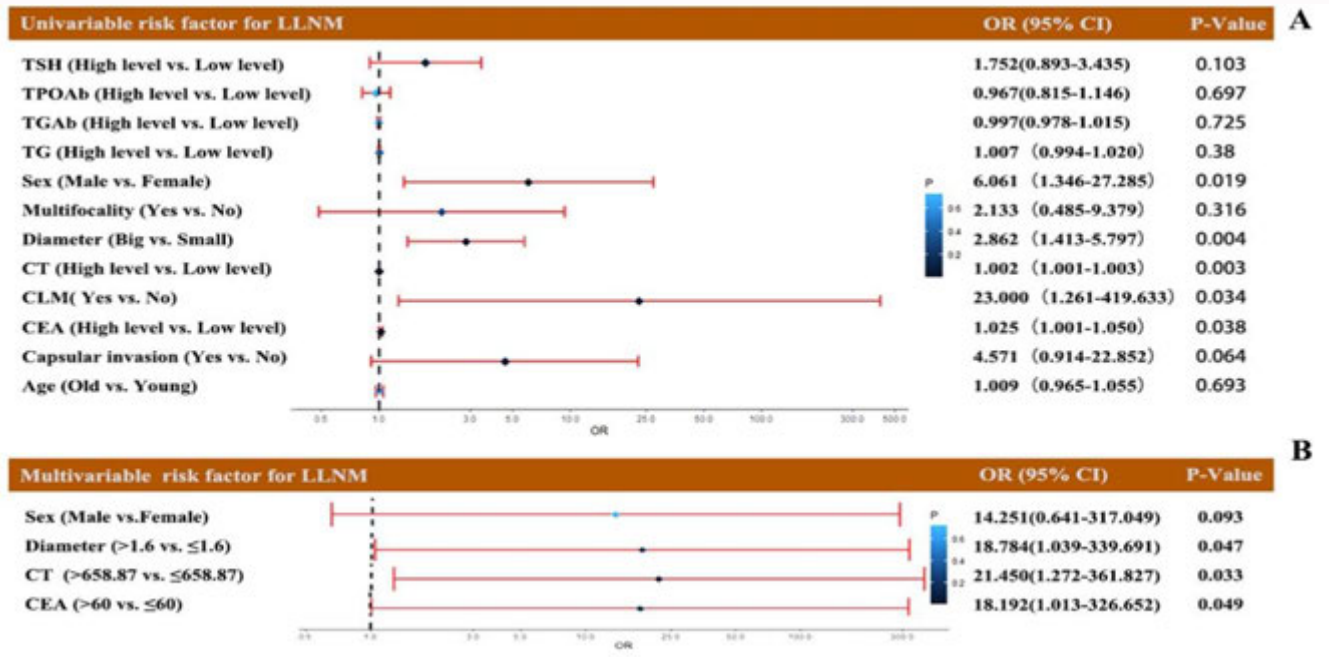

Figure 2: Univariate (A) and multivariate (B) logistic regression of factors associated with LLNM.
CT: Calcitonin; CEA: Carcinoembryonic Antigen; TG: Thyroglobulin; TSH: Thyroid Stimulating Hormone; TGAb: Antibodies against Thyroglobulin; TPOAb: Antibodies against Thyroperoxidase; CNM: Central Lymph Node Metastasis; LLNM: Lateral Lymph Node Metastasis; OR: Odds Ratio; CI: Confidence Interval

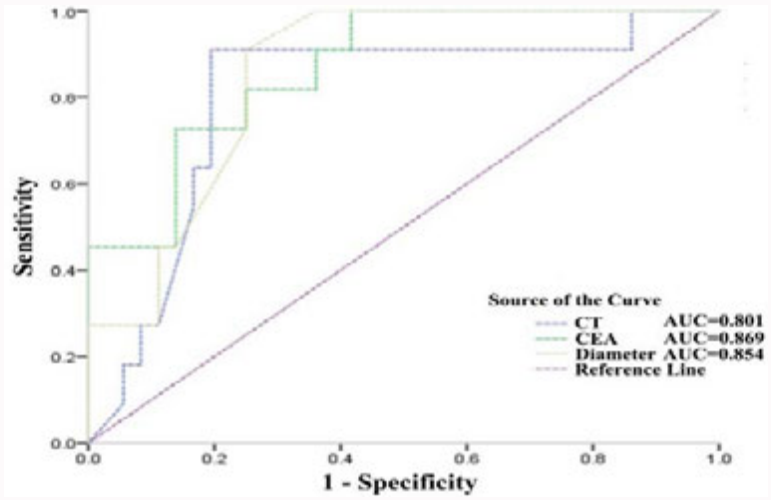

Figure 3: ROC Curves of CT, CEA, Diameter detection for LLNM of medullary thyroid carcinoma patients.
CT: Calcitonin; CEA: Carcinoembryonic Antigen; LLNM: Lateral Lymph Node Metastasis

value as the cut-off value (60 ng/mL). Moreover, multivariate analysis was performed using binary logistic regression to determine the predictive factor for LLNM of MTC patients (Figure 2B). Diameter >1.6 cm, CT>658.87 pg/mL, CEA>60 ng/mL were considered to be the independent risk factors predicting the occurrence of LLNM of MTC patients ($P_{Diameter}$=0.047, Odds Ratio (OR) =18.787, 95% Confidence Interval (95% CI): 1.039-399.691; P_{CT}=0.033, OR=21.450, 95% CI: 1.272-361.827; P_{CEA}=0.049, OR=18.192, 95% CI: 1.013-326.652, respectively).

Nomogram for predicting likelihood of LLNM in MTC patients

Based on the independent factors screened through multivariate analysis, we established a nomogram for predicting likelihood of LLNM in MTC patients, including diameter, CT, CEA in this predicting model (The total score and the score of each risk factor were shown in Figure 4). The C-index was 0.961 (95% CI, 0.916-1). ROC curve and AUC were presented in Figure 5A. Furthermore, we drew the calibration curve of the nomogram for predicting LLNM after 1,000 bootstrapping (Figure 5B). The external validation population comprised of 16 patients with 31.25% (5 patients) rate of LLNM. When applied to the original model, the external validation dataset produced a C-index of 0.968 (95% CI, 0.904-1) (Figure 6), which proving that these factors were significant. A DCA was performed to evaluated the predictive ability of our nomogram. As shown in Figure 7, the predictive ability of our nomogram was favorable in detecting LLNM for MTC patients.

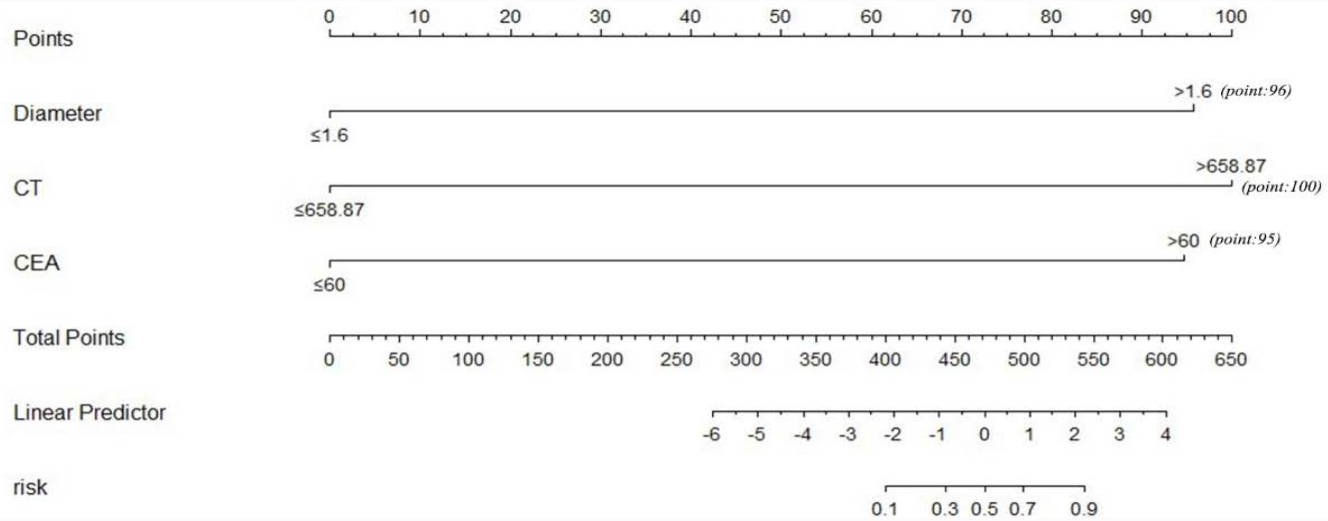

Figure 4: The nomogram for predicting risk of possible LLNM in medullary thyroid carcinoma patients.
CT: Calcitonin; CEA: Carcinoembryonic Antigen; LLNM: Lateral Lymph Node Metastasis

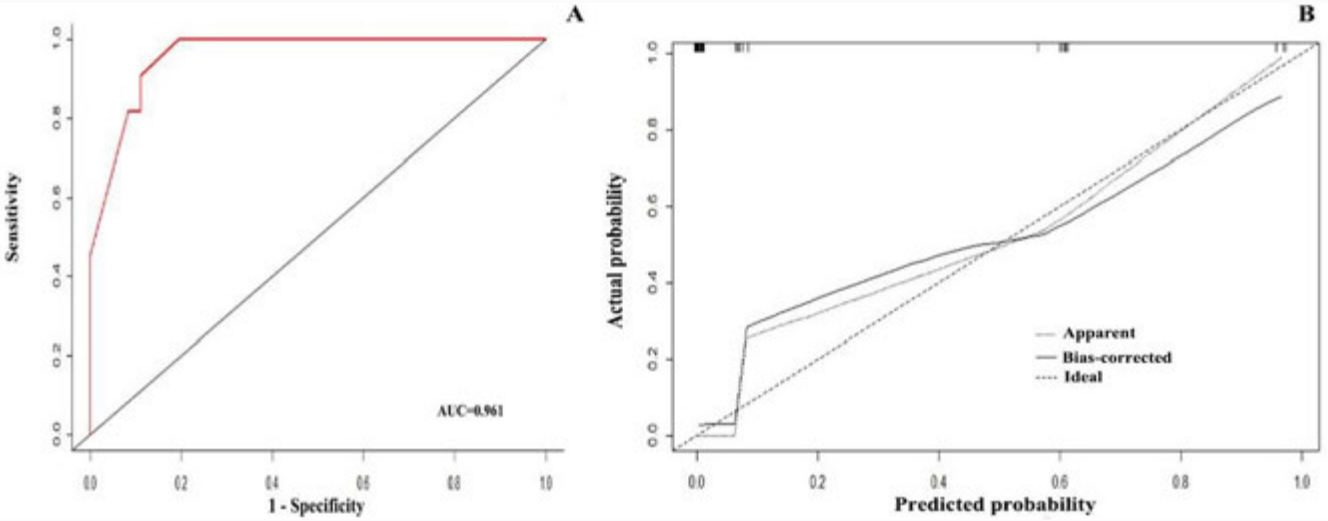

Figure 5: Evaluation and Validation of the nomogram. (A) The receiver operating characteristics (ROC) curve and area under the ROC curve (AUC) of the nomogram. (B) The calibration curve of the nomogram for predicting Lateral Lymph Node Metastasis (LLNM). Actual probability is plotted on the y-axis, and nomogram predicted probability on the x-axis.

Discussion

Surgery is the only curative treatment for MTC, which is recommended to remove all lesions in the neck. Total thyroidectomy and CLND are recommended by international guidelines for MTC, because MTC can metastasize early and cause significant morbidity. LLND is needed for cN1b patients (metastasis in other unilateral, bilateral or contralateral cervical compartments) and tumor recurrence, but the necessity for cN0 MTC patients to undergo prophylactic ipsilateral or bilateral LLND is still controversial. Further, LLNM was the risk factor of recurrence and poor prognosis, which recommend surgeons to pay more attention to assess lymph node metastasis and develop a suitable extent for initial surgery. In this study, we observed that CEA>11.23 ng/mL was a significant risk factor to predict CNM of MTC patients. Further, diameter >1.6 cm, CT>658.87 pg/mL, CEA>60 ng/mL were considered to be the independent risk factors predicting the occurrence of LLNM of MTC patients, which was consistent with previous studies.

CT was a sensitive serum biomarker to predict CNM and LLNM of MTC patients, which could be considered to decide the extent of MTC patients. In this study, we observed preoperative serum CT level thresholds of 219.85 pg/ml and 658.87 pg/ml were associated with the presence of CNM and LLNM, and previous studies have shown the same findings. Bae et al. [5] described that CT level higher than 226.6 pg/ml and 755.0 pg/ml linked to the occurrence of CNM and LLNM in MTC patients, and Park et al. [6] reported, preoperative calcitonin thresholds of 20 pg/ml and 200 pg/ml were associated with the presence of ipsilateral LNM and contralateral LNM. Ye et al. [7] recommended that the cutoff of serum CT for predicting LLNM of MTC patients was 303.1 pg/ml, with the AUC up to 0.867 (Sensitivity 94.4%, Specificity 73.7%). Further, based on multivariate analysis, CT was considered to be an independent risk factor predicting the occurrence of LLNM of MTC patients, which could serve as a biomarker for surgeons in deciding the extent and treatment.

CEA was a tumor marker mainly expressed in gastrointestinal

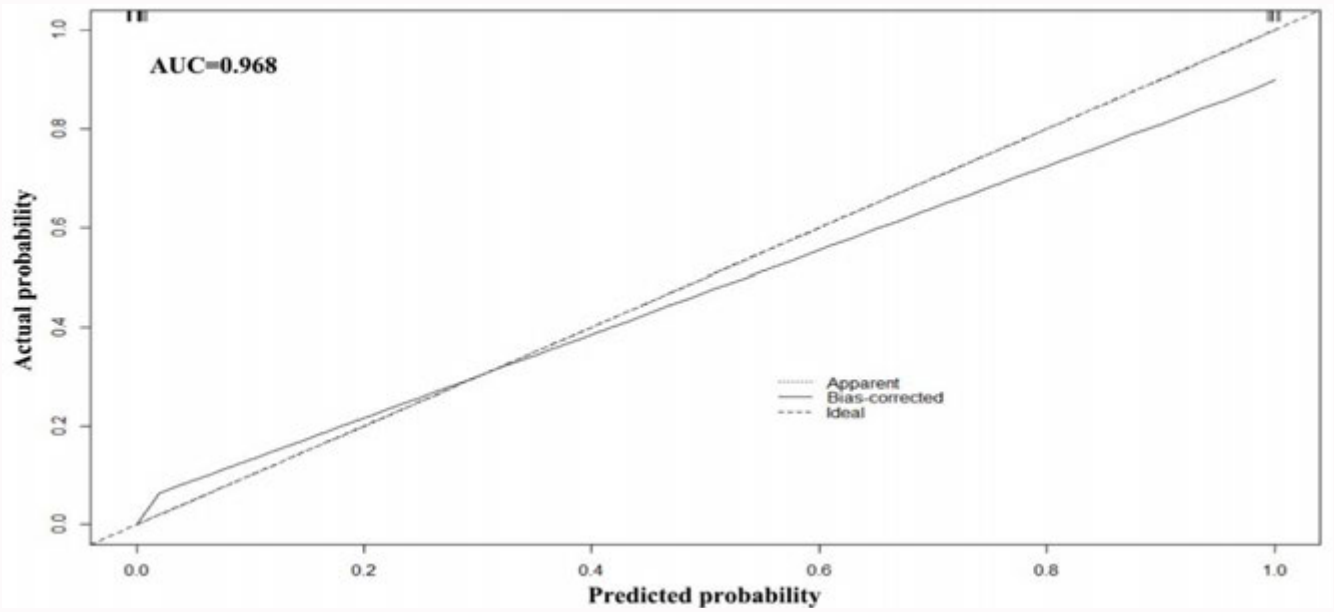

Figure 6: The calibration curve of the nomogram for external validation dataset. The C-index was 0.968 (95% CI, 0.904-1).

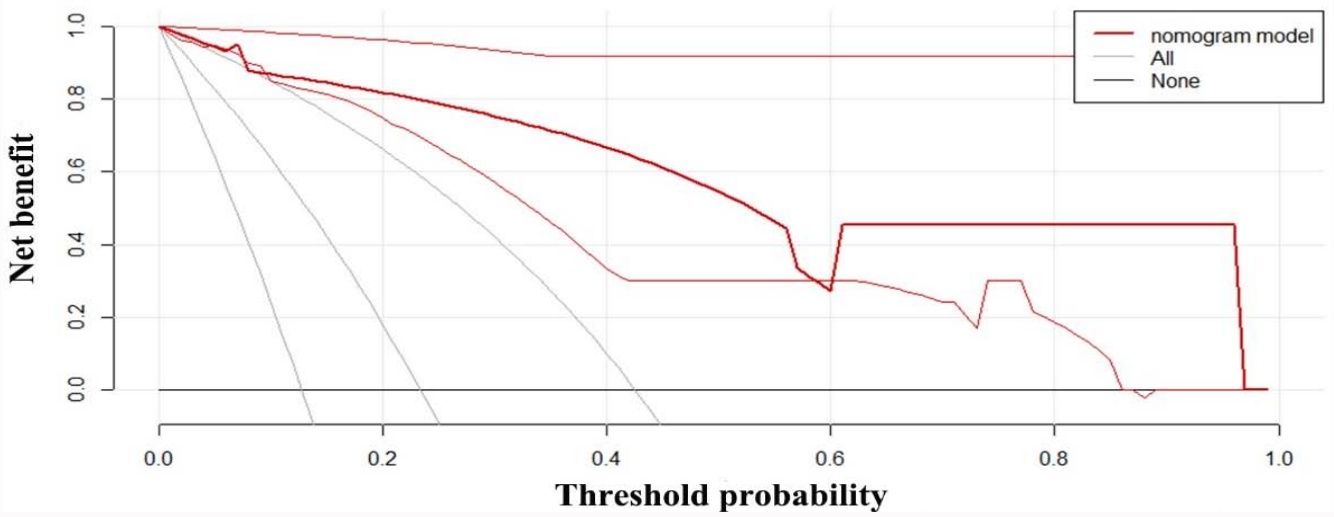

Figure 7: Decision curve analysis for nomogram in predicting Lateral Lymph Node Metastasis (LLNM) in medullary thyroid carcinoma patients.

tumors, which was also synthesized and secreted by parafollicular C cells originating from the endoderm of the primitive anterior gut [8,9]. The clinical implications of lower CEA concentrations are unclear [4]. However, as Passos et al. [10] shown, preoperative CEA values >30 ng/mL indicated extra-thyroid disease, while CEA values >100 ng/mL are associated with lymph node involvement and distant metastases. Ye et al. [7] recommended that the cutoff of serum CEA for predicting LLNM of MTC patients was 29.8 ng/mL, with the AUC up to 0.831 (Sensitivity 75.0%, Specificity 81.57%). Fan et al. reported [11], preoperative CEA values ≥ 30 ng/mL were statistically significant for the presence of CNM of MTC patients. In line with previous studies, we observed preoperative serum CEA level thresholds of 11.23 ng/mL and 24.1 ng/mL were associated with the presence of CLNM and LLNM, and multivariate analysis indicated CEA>60 ng/mL was an independent risk factor predicting the occurrence of LLNM.

In our study, we found that MTC patients with diameter >1 cm had a higher proportion of CNM and LLNM, which was significantly different from patients with diameter ≤ 1 cm. Further, multivariate analysis indicated diameter was an independent risk factor predicting the occurrence of LLNM. In a cohort of 5,817 consecutive patients with thyroid nodules, Costante et al. [12] reported a statistically significant relationship between larger diameter and higher preoperative serum CT level, which indicated higher tumor burden and lymph node metastasis. Similar conclusions were drawn in other reports [6,13]. According to National Comprehensive Cancer Network (NCCN) guidelines [14], when primary tumor size larger than 1 cm, total thyroidectomy with CLND was recommended. Since neck ultrasound is widely used in clinical practice, we recommend diameter as the important risk factor to predict LLNM in MTC patients.

Besides the above risk factors, we also found some auxiliary risk

factors. Capsular invasion was associated with tumor aggressiveness of MTC and LNM, as shown by various studies [11,13,15], which was inconsistent with our analysis. TG was a tumor marker produced in the thyroid gland, which was used in the follow-up and management of patients with DTC [16]. Seib et al. [17] reported TG as an indicator to identify MTC patients with remnant thyroid tissue after prophylactic thyroidectomy. However, we found that preoperative serum TG was not significant in MTC patients with lymph node metastasis.

There are some limitations to our study. Firstly, the sample size in our study was relatively small since the incidence of MTC is much lower than DTC. Secondly, we retrospectively analyzed the clinicopathological features of the recruited patients. There may be an inevitable selection bias. Prospective studies are needed to support our findings. Besides, the data related to RET gene were not collected in this paper, which would be an important direction of follow-up research for us.

Conclusion

To conclude, diameter, CT and CEA are significant risk factors to predict LLNM in MTC patients. A nomogram was made to predict the probability, which would help surgeons make appropriate therapeutic decisions.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
2. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30(12):1856-83.
3. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. American Thyroid Association Guidelines task force on medullary thyroid carcinoma. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610.
4. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Ba GG, et al. British Thyroid Association. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122.
5. Bae SY, Jung SP, Choe JH, Kim JS, Kim JH, et al. Prediction of lateral neck lymph node metastasis according to preoperative calcitonin level and tumor size for medullary thyroid carcinoma. Kaohsiung J Med Sci. 2019;35(12):772-7.
6. Park H, Park J, Choi MS, Kim J, Kim H, Shin JH, et al. Preoperative serum calcitonin and its correlation with extent of lymph node metastasis in medullary thyroid carcinoma. Cancers (Basel). 2020;12(10):2894.
7. Ye L, Zhou X, Lu J, Wang Y, Xie X, Zhang J, et al. Combining serum calcitonin, carcinoembryonic antigen, and neuron-specific enolase to predict lateral lymph node metastasis in medullary thyroid carcinoma. J Clin Lab Anal. 2020;34(7):e23278.
8. Oczko-Wojciechowska M, Czarniecka A, Gawlik T, Jarzab B, Krajewska J. Current status of the prognostic molecular markers in medullary thyroid carcinoma. Endocr Connect. 2020;9(12):R251-63.
9. May CL, Kaestner KH. Gut endocrine cell development. Mol Cell Endocrinol. 2010;323(1):70-5.
10. Passos I, Stefanidou E, Meditskou-Eythymiadou S, Mironidou-Tzouveleki M, Manaki V, Magra V, et al. A review of the significance in measuring preoperative and postoperative Carcinoembryonic Antigen (CEA) values in patients with Medullary Thyroid Carcinoma (MTC). Medicina (Kaunas). 2021;57(6):609.
11. Fan W, Xiao C, Wu F. Analysis of risk factors for cervical lymph node metastases in patients with sporadic medullary thyroid carcinoma. J Int Med Res. 2018;46(5):1982-9.
12. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92(2):450-5.
13. Zhou TH, Zhao LQ, Zhang Y, Wu F, Lu KN, Mao LL, et al. The prediction of metastases of lateral cervical lymph node in medullary thyroid carcinoma. Front Endocrinol (Lausanne). 2021;12:741289.
14. Haddad RI, Bischoff L, Ball D, Bernet V, Blomain E, Busaidy NL, et al. Thyroid Carcinoma, Version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20(8):925-51.
15. Oh HS, Kwon H, Song E, Jeon MJ, Song DE, Kim TY, et al. Preoperative clinical and sonographic predictors for lateral cervical lymph node metastases in sporadic medullary thyroid carcinoma. Thyroid. 2018;28(3):362-8.
16. Algeciras-Schimnich A. Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018;55(3):205-18.
17. Seib CD, Harari A, Conte FA, Duh QY, Clark OH, Gosnell JE. Utility of serum thyroglobulin measurements after prophylactic thyroidectomy in patients with hereditary medullary thyroid cancer. Surgery. 2014 Aug;156(2):394-8.