

# A nomogram to predict skip metastasis in papillary thyroid cancer

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## Research

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# Abstract

## Background

Skip metastases are defined as lateral lymph node metastasis (LNM) without the involvement of central LNM in papillary thyroid cancer (PTC), and it is difficult to predict in clinical practice. Our study aimed to investigate the risk factors of skip metastasis and establish a nomogram for predicting the probability of skip metastasis in PTC patients.

## Patients and Methods

A total of 378 consecutive PTC patients with clinically suspected LNM who underwent modified radical neck dissection (MRND) from March 2018 to July 2019 were enrolled in our hospital, Univariate and multivariate analyses were used to examine risk factors of skip metastasis, and a nomogram prediction model was established and internal validated.

## Results

The incidence of skip metastasis was 11.9% (45/378). Primary tumor size  $\leq 1$ cm (OR=2.703, 95%CI, 1.342-5.464; P =0.005), Age (OR=1.051, 95%CI, 1.017-1.805, P =0.005), Primary tumor location in the upper portion (OR=6.799, 95%CI, 2.710-17.060, P <0.001) were found to be independent risk factors for skip metastasis in PTC patients. A nomogram based upon these predictors performed well. With an area under the curve (AUC) of 0.806 (95%CI, 0.736-0.876) and the P value of the Hosmer-Lemeshow goodness of fit test was 0.66, Decision curve analysis revealed that nomogram was clinically useful.

## Conclusion

Based on the risk factors of skip metastasis and established a high-performance nomogram, which can provide an individual risk assessment and guide treatment decisions for patients.

## Background

The worldwide incidence of papillary thyroid carcinoma (PTC) has been steadily increasing in recent years[1]. In China, PTC is the most common malignant tumor in women under 30 years old, its incidence rate ranks 8th in women[2, 3]. PTC often disseminates into cervical lymph nodes with a reported incidence from 30% to 80 % at the first diagnosis[4, 5], cervical lymph nodes metastasis (LNM) is an important factor affecting local recurrence of PTC and long-term survival of patients[6, 7]. Generally, LNM of PTC occurs in a stepwise fashion, spreading from the thyroid lobes. LNM in PTC involves the central lymph node (CLN) first, then to the ipsilateral lateral lymph node (LLN), and finally arriving to the contralateral LLN and mediastinal compartment[8]. However, not all patients with PTC follow the drainage pathway for metastasis. Some patients develop lateral LNM without the involvement of central LNM *via* histopathological diagnosis, which is referred to as "skip metastasis"[6, 9, 10]. The rate of skip metastasis in PTC ranged from 1.6% to 21.8%[11-13]. The significance of skip metastasis in patients with

PTC is still unclear. However, if untreated, there will increase the risk of locoregional recurrence and distant metastasis, reoperation and I<sup>131</sup> therapy to treat locoregional recurrence or distant metastasis may affect patient's quality of life. Thus, it is necessary for surgeons to identify the risk factors of skip metastasis before surgery and subsequent surgical intervention are important in preventing locoregional recurrence. In clinical work, the diagnosis of lateral neck LNM relies on ultrasound firstly, and then fine needle aspiration cytology (FNAC), thyroglobulin, or BRAF-V600E detection are only recommended for suspicious LLN. However, ultrasound has high specificity and low sensitivity in the diagnosis of cervical LNM[14, 15]. For patients with no enlarged lymph nodes in the central compartment before surgery, ultrasound doctors often relax their vigilance in the assessment of lateral lymph nodes and omit skip metastasis easily. Previous study[13, 16-18] reported that tumor located in the upper portion and tumor diameter no larger than 1cm were closely linked to skip metastasis, and suggested that patients with the above risk factors should be carefully evaluated for lymph node status. Unfortunately, it was not given the probability of skip metastasis in these patients, and what kind of patients needed to undergo prophylactic LLN dissection.

To address this, our study first established an individual nomogram model for predicting skip metastasis. The nomogram is a practical and simple tool for identifying high-risk patients and quantifying the individual risk, which has been frequently reported in cancer research[19-22]. The aim of this study was to develop a nomogram to predict skip metastasis in PTC patients, and provide an individual risk assessment and guide treatment decisions for patients.

## Patients And Methods

### Patients

This study retrospectively reviewed the clinical records of 401 patients who underwent modified radical neck dissection (MRND) from March 2018 to July 2019 in our hospital. Inclusion criteria as follows: (I) PTC patients with complete medical records. (II) PTC patients with clinically suspected LNM preoperative who underwent MRND, and postoperative histopathology confirmed PTC with lateral LNM. The exclusion criteria for this study were as follows: (I). Family history of thyroid cancer. (II). History of neck surgery. (III). Patients who underwent iodine 131 before surgery. (IV). Tumor located in the isthmus. After strict inclusion and exclusion criteria, a total of 378 patients met the requirements. All patients knew and agreed to the treatment plan. Our study was approved by the Ethics Committee of Xiangya Hospital of Central South University.

### Surgery techniques

Ultrasound (US) and enhanced computed tomography (CT) were routinely performed in this study to assess the cervical lymph nodes and thyroid nodules before surgery, FNAB was systematically performed in our hospital. If the intraoperative frozen pathological examination is confirmed as PTC, prophylactic CLN dissection was conducted after total thyroidectomy. The CLN dissection ranged from the superiorly

by the hyoid bone, inferiorly to the sternal notch, and lateral to the carotid sheath, posteriorly to prevertebral fascia, including pretracheal, prelaryngeal (Delphian), perithyroidal and paratracheal nodes. Lateral compartment includes levels Ⅷ-Ⅹ, if lateral LNM was proved by FNAB or evident on preoperative US and enhanced CT, MRND would be performed. while sparing the sternocleidomastoid muscle, internal jugular arteriovenous, spinal accessory nerve and other important structures, the lateral compartment delimited inferiorly to the subclavian vein, superiorly to the sublingual nerve, and lateral to the anterior edge of the trapezius muscle. All specimens were sent to the Department of Pathology, the histopathological evaluation of these specimens was conducted by pathologists with at least 8 years of experience and diagnosed more than 400 PTC cases.

### **Clinicopathological properties**

Clinicopathological variables such as gender, age, primary tumor size, total tumor size, primary tumor location, tumor extension, multifocality, bilaterality, extrathyroidal extension (ETE), capsule invasion, Hashimoto's thyroiditis (HT), number of central dissected lymph node and number of lateral dissected lymph nodes involvement. Primary tumor location was divided into three parts (upper, middle, and lower) which based on the thyroid lobe involved. Primary tumor size was defined as the largest tumor in the specimen. Total tumor size means the sum of all tumor diameters in the specimen. Tumor extension was classified to four stages (T1, T2, T3 and T4) following the American Thyroid Association 2015 guidelines. Multifocality means two or more tumors lesion in the thyroid. Bilaterality is defined as the presence of carcinoma in both thyroid lobes. ETE was regarded as the tumor penetrates through the capsule and invades skeletal muscle tissue or perithyroidal soft tissue. In contrast, capsule invasion was defined as the tumor invades into the thyroid capsule but does not penetrate it. The HT patient was diagnosed by pathological examination.

### **Statistical analyses**

Statistical analysis was performed using SPSS (19.0 version) and R software (version 3.4.2), all tests were two-sided, and  $P < 0.05$  was considered statistically significant. Categorical variables were expressed as percentage (%) and frequency, the fisher exact test and chi-square test or were used for categorical variables. Continuous variables were expressed as the mean  $\pm$  SD, Continuous variables were compared using the t-test or Mann-Whitney U test. We performed multivariate analysis was performed to screen for significant predictors of skip metastasis. Combined the significant predictive predictors based on multivariate analysis and developed a nomogram. the nomogram model was calibrated using a calibration plot and Hosmer-Lemeshow goodness-of-fit test ( $P > 0.05$ ), C-index values and ROC curves were used to test its discrimination. The area under the curve (AUC) was calculated. The calibration plot with bootstrapping was used to illustrate the association between the predicted probability and actual probability. The clinical usefulness of nomogram was evaluated using the decisions curve analysis.  $P < 0.05$  was regarded as statistically significant.

## **Results**

## Patients Characteristics.

A total of 378 patients were enrolled in this study. There were 264 females and 114 males patients and the ratio of female to male is 2.32:1. The age of the patients ranged from 10 to 72 years, and the mean age of 39.96 years. 88.89% of patients are younger than 55 years old; Among all patients, 95(25.13%) patients exhibited capsule invasion, and 69(18.25%) patients presented ETE. Bilaterality was detected in 119(30.95%) patients and HT was detected in 87(23.16%) patients. Multifocal tumors (n=84(22.22%)) were less common than solitary tumors (n=294(77.78%)). Primary tumor location was divided into upper (n= 92), middle (n= 180), and lower portion (n =106). According to the American Thyroid Association 2015 guidelines, T1, T2, T3 and T4 were found in 219, 48, 83 and 28 patients, respectively. The primary tumor size less than 1cm was detected in 142 patients. The mean number of total central neck lymph nodes and lateral neck lymph nodes was  $7.51 \pm 5.08$ ,  $18.25 \pm 12.59$ , respectively. (Table 1).

Among all patients, 45 (11.9%) patients were presented skip metastasis as lateral LNM without central LNM. The distributions of skip metastasis are shown in Table 2, The single-level metastasis(n=21) was the most common pattern for lateral LNM, followed by double-level metastasis(n=16), triple-level metastasis(n=7) and four-level metastasis(n=1). A further analysis showed that the level III and IV were the most involved sites whether in single-level metastasis or double-level metastasis. (Table 2)

### Table 1: Demographics and clinical characteristics of PTC patients(n=378)

Variable	Results
Sex	
male	114(30.16%)
female	264(69.84%)
Age	
$\geq 55$ years	42(11.11%)
<55 years	336(88.89%)
Age (mean $\pm$ SD, years)	39.96 $\pm$ 11.73
Multifocality	
Yes	84(22.22%)
No	294(77.78%)
Bilaterality	
Yes	117(30.95%)
No	261(69.05%)
Primary tumor location	
Upper	92(24.34%)
Middle	180(47.62%)
lower	106 (28.04%)
HT	
Yes	87(23.16%)
No	291(76.98%)
ETE	
Yes	69(18.25%)
No	309(81.75%)
Capsule invasion	
Yes	95(25.13%)
No	291(76.98%)
Tumor extension	
T1	219(57.94%)
T2	48(12.70%)
T3	83(21.96%)
T4	28(7.41%)
Primary tumor size $\leq$ 1cm	
Yes	142(37.57%)
No	236(62.43%)
Total tumor size (mean $\pm$ SD, cm)	1.56 $\pm$ 0.96
Skip metastasis	
Yes	45(62.43%)
No	333(62.43%)

Number of central dissected lymph nodes	7.51± 5.08
Number of lateral dissected lymph nodes	18.25±12.59

Abbreviations: HT: Hashimoto’s thyroiditis; ETE: extrathyroidal extension; SD: standard deviation;

**Table 2: Distribution of skip metastasis**

Neck level	No
Single level (n = 21)	
I	2
II	10
III	9
Double level (n = 16)	
I + II	4
I + III	1
II + III	9
I + II + III	1
I + II + III	1
Triple level (n = 7)	
I + II + III	4
I + II + III	3
Four level (n = 1)	
I + II + III + IV	1
Total	45

### Clinicopathologic risk factors for skip metastasis

Univariate analysis demonstrated that age, primary tumor location, Primary tumor size  $\leq 1$ cm were associated with skip metastasis (all  $P \geq 0.05$ ). The age in patients with skip metastasis were significantly older than the patients with absented skip metastasis ( $44.48 \pm 12.556$  vs.  $39.37 \pm 11.509$ ,  $P = 0.006$ ). When the primary located in the superior, middle, inferior portion of the thyroid, the incidence of skip metastasis

was 7.41%, 2.38%, 1.85%, respectively. In addition, the primary tumor size not larger than 1cm was more frequent in skip metastasis (54.55% vs.35.33%,  $P=0.013$ ). (Table 3).

To identify the independent risk factors of skip metastasis in PTC patients, variables with statistical differences were incorporated in multivariate analysis. We found that Primary tumor size  $\leq 1$ cm(OR=2.703, 95%CI,1.342-5.464;  $P=0.005$ ), Primary tumor location in the upper portion(OR=6.799, 95%CI, 2.710-17.060,  $P<0.001$ ), Age(OR=1.051, 95%CI,1.017-1.805,  $P=0.005$ )were found to be independent factors for skip metastasis in PTC patients.(Table 4).

**Table 3: Univariate analysis of risk factors for skip metastasis in PTC patients**

Variable	Skip metastasis		$\chi^2/t$	P-value
	Present(n=45)	Absent(n=333)		
Sex (male/female)	9/35	105/229	2.23	0.136
Age( $\geq 55$ years/<55 years)	8/36	34/300	2.52	0.112
Age	44.48 $\pm$ 12.56	39.37 $\pm$ 11.51	2.74	0.006
Multifocality (Yes/No)	7/37	77/257	1.15	0.284
Bilaterality (Yes/No)	16/28	101/233	0.68	0.409
Primary tumor location upper/middle/lower	28/9/7	64/171/99	41.93	<0.001
HT(Yes/No)	9/35	78/256	0.18	0.668
ETE(Yes/No)	8/36	61/273	0.001	0.989
Capsule invasion (Yes/No)	11/33	84/258	0.001	0.983
Tumor extension(T1/T2/T3/T4)	23/7/12/2	196/41/71/26	1.87	0.6
Primary tumor size $\leq 1$ cm (Yes/No)	24/20	118/216	6.12	0.013
Total tumor size/cm	1.31 $\pm$ 0.87	1.59 $\pm$ 0.97	1.79	0.075
Number of central dissected lymph nodes	6.47 $\pm$ 4.59	7.65 $\pm$ 5.14	1.46	0.144
Number of lateral dissected lymph nodes	16.89 $\pm$ 10.12	18.44.47 $\pm$ 12.98	0.77	0.439

Abbreviations: HT: Hashimoto's thyroiditis; ETE: extrathyroidal extension;

**Table 4 Multivariate analysis of risk factors for skip metastasis in PTC patients**

Variable	OR (95% CI)	P-value
Age	1.051(1.017-1.805)	0.003
Primary tumor location		
Lower as reference		
Middle	0.678(0.241-1.912)	0.463
upper	6.799(2.710-17.060)	<0.001
Primary tumor size $\leq 1$ cm (Yes/No)	2.703(1.342-5.464)	0.005

### Construction of an Individualized Prediction Model

Based on the results of multivariate analysis, we established a nomogram model for predicting skip metastasis, As shown in Figure 1. We can predict the probability of skip metastasis in patients by summing the scores of each variable. Older patients, Primary tumor location in the upper portion and Primary tumor size  $\leq 1$ cm had higher scores. For example, a 55-years-old (69 points) PTC patient with a 7mm tumor (31points) located in the upper portion(72points), has a about 60% possibility (total points,172) of skip metastasis. The risk of skip metastasis predicted by this nomogram ranged from 0.01 to 0.8.

### Model performance and clinical utility of the nomogram

To test its consistency and discrimination, the nomogram model was calibrated by Hosmer-Lemeshow goodness-of-fit test and calibration plot. the internal calibration plot showed a mostly perfect agreement between the predicted and actual results of the nomogram model, as shown in Figure 2. The Hosmer-Lemeshow goodness-of-fit test also showed an excellent concordance between the predicted and actual outcomes ( $\chi^2=5.89$ ,  $df=8$ ,  $p=0.66$ ). ROC curves and C-index values were used to test the discrimination of the nomogram model, The C-index value is 0.806 and an area under the curve (AUC) of 0.806 (95% CI, 0.736–0.876) indicated good discrimination of the model (Figure 3). In the decision curve analysis (DCA) curve, when the skip metastasis of threshold probability was ranged from 0.04 to 0.78, the nomogram model achieved a greater net benefit than the “None” or “All”. (Figure 4).

Nomograms show the likelihood of skip metastasis as a percentage, we assigned a Youden-derived cutoff value to the nomogram. The optimal cutoff value was -2.374. (sensitivity: 79.5%; specificity: 67.7%; accuracy: 69.0%; negative predictive value: 96.2%; positive predictive value: 24.5%).

## Discussion

Cervical LNM was common in PTC patients and accounts for 30%-80%[4, 5, 21], LNM was associated with local recurrence PTC and overall mortality of patients[6, 7]. Reoperation for PTC recurrence may increase the operative complication and have a negative effect on patient's quality of life. Thus, it is important for surgeons to perform precisely preoperative evaluation and prediction for LNM to take an appropriate surgical management strategy. "Skip metastasis" was defined as lateral LNM without the involvement of central LNM, which is not uncommon in clinical practice and difficult to predict[11, 13, 16, 22, 23]. In this study, we developed an individualized nomogram to evaluate the likelihood of skip metastasis in patients with PTC based on the pathologic and clinical characteristics, which is consistent with the current trend toward personalized and precision medicine.

The incidence of skip metastasis ranges from 1.6% to 21.8%, which could be explained by different regions and sample sizes[15, 24]. However, the previous studies were limited by low patient numbers and the heterogeneous patient population[10, 14, 22]. Our study used a sufficient number of patients (n=378) and the rate of skip metastasis was 11.9%, which is in accordance with previous study. The mechanism of skip metastasis is still unclear. Machens et al[22] summarized the clinical data of 13 patients with skip metastasis of PTC and proposed that skip metastasis is an unstable lymph node metastasis phenomenon of thyroid cancer, which is a rare and occasional metastatic mode, not due to the limited or missed lymph node samples. skip metastases showed most frequently single-level metastases in the lateral compartment and less multiple-level metastasis, and level III nodes were the most frequently involved sites, followed by Levels IV, II and V[14-16].

Next, we explored the predictive factors associated with skip metastasis in PTC. In the univariate analyses, we found that age, primary tumor location and primary tumor size  $\leq 1$  cm were significantly related with skip metastasis in PTC patients (all  $P \leq 0.05$ ). These variables were also the independent predictors of skip metastasis, and their predictive value was verified by multivariate analysis, while gender, total tumor size, tumor extension, multifocality, bilaterality, ETE, HT, capsule invasion were not significantly associated with skip metastasis (all  $P \geq 0.05$ ) (tables 2 and 3). In this study, Patients with primary tumor location in the upper portion were more likely to have skip metastasis, which is in line with previous reports[13, 16, 24]. This predictive factor could be explained by the anatomical structure of the lymphatic drainage system. However, Lim et al[10] reported that the primary tumor location in the upper pole was inversely correlated with skip metastasis. The relationship between skip metastasis and tumor location remain controversial and need to further research. In addition, the primary tumor size not larger than 1 cm was more frequent in skip metastasis (54.55% vs. 35.33%,  $P=0.013$ ), these results may remind us that the primary tumor size is important factor for predicting skip metastasis, we should be carefully evaluated lateral lymph nodes status when tumor size no larger than 1 cm. Previous literatures also revealed that skip metastasis was more common in less aggressive forms of PTC[16]. Furthermore, this study demonstrated that the risk of skip metastasis is associated with age, increasing age was significantly related with an increased risk of skip metastasis ( $44.48 \pm 12.556$  vs.  $39.37 \pm 11.509$ ,  $P=0.006$ ), and this finding has never been reported in previous studies. According to the 8th American Joint Committee on Cancer (AJCC) TNM staging system[25], 55 years old was cut-off value and patients aging

$\geq 55$  could have higher risk factors for LNM. However, we did not find that age more than 55 years was related with skip metastasis.

Based on the abovementioned significant factors related with skip metastasis in PTC, a predictive nomogram was constructed. To date, there is no report on the use of nomogram to predict skip metastasis. This study summarized clinical data and first established a nomogram that performed well in the prediction of skip metastasis. The calibration plots showed good agreement between predicted probability and actual probability of skip metastasis. Likewise, the AUC of nomogram in this study was 0.806 (95% CI, 0.736–0.876), according to previous studies, an AUC value greater than 0.7 have superior accuracy, indicating good discrimination. Clinical decision curve analysis demonstrated that most of PTC patients can benefit from the predictive model. Thus, utilization of this nomogram can provide an individual risk assessment and guide treatment decisions for patients. With the optimal cutoff value, the nomogram yielded 79.5% sensitivity, 67.7% specificity, the maximum at the probability of skip metastasis was 0.085, corresponding to a total point value of 83.04. Therefore, Patients with a total point of more than 83.04 are considered to be high risk patients with skip metastasis. and the MRND is considered. However, for patients with a total point value less than 83.04, close observation with US and follow-up are recommended. Therefore, we confirmed that our nomogram was an objective and useful tool to aid clinicians decide whether to perform MRND rather than making a decision based on rough and simple clinicopathological Characteristics.

However, our nomogram has several limitations. Firstly, this study was a retrospective, single-center research which may result in selection bias and information bias, the dataset cannot represent the whole PTC population. Secondly, the validation of our nomogram was only conducted internally, external validation should be performed to ensure that it has better extrapolation. Thirdly, although our nomogram may identify patients at high risk of skip metastasis, whether undergoing MRND is beneficial for improving long-survival still unknown. Despite these shortcomings, our nomogram was based on the reliable clinical data obtained from patients with satisfactory manifestations of a good discriminative ability and internal validation.

## Conclusion

In conclusion, we developed a predictive nomogram for skip metastasis in PTC patients, and the nomogram can help identify patients at high risk of skip metastasis who need to undergo MRND. Thus, utilization of this nomogram can provide an individual risk assessment and guide treatment decisions for patients.

## Abbreviations

LNM: lateral lymph node metastasis; PTC: papillary thyroid cancer; CLN: central lymph node; LLN: lateral lymph node; US: ultrasound; CT: enhanced computed tomography; MRND: modified radical neck dissection; HT: Hashimoto's thyroiditis; ETE: extrathyroidal extension; SD: standard deviation; ROC:

Receiver operating characteristic; AUC: Area under curve; DCA: decision curve analysis; AJCC: American Joint Committee on Cancer.

## **Declarations**

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### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Author contributions**

Qianhui Ouyang: Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript.

Wenlong Wang: Conception and design, Provision of study patients, Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript.

### **Ethics approval and consent to participate**

This study was a retrospective study. And the study protocols were approved by the Ethics Committee of Xiangya Hospital, Central South University (Changsha, China).

### **Consent for publication**

Not applicable.

## Competing interests

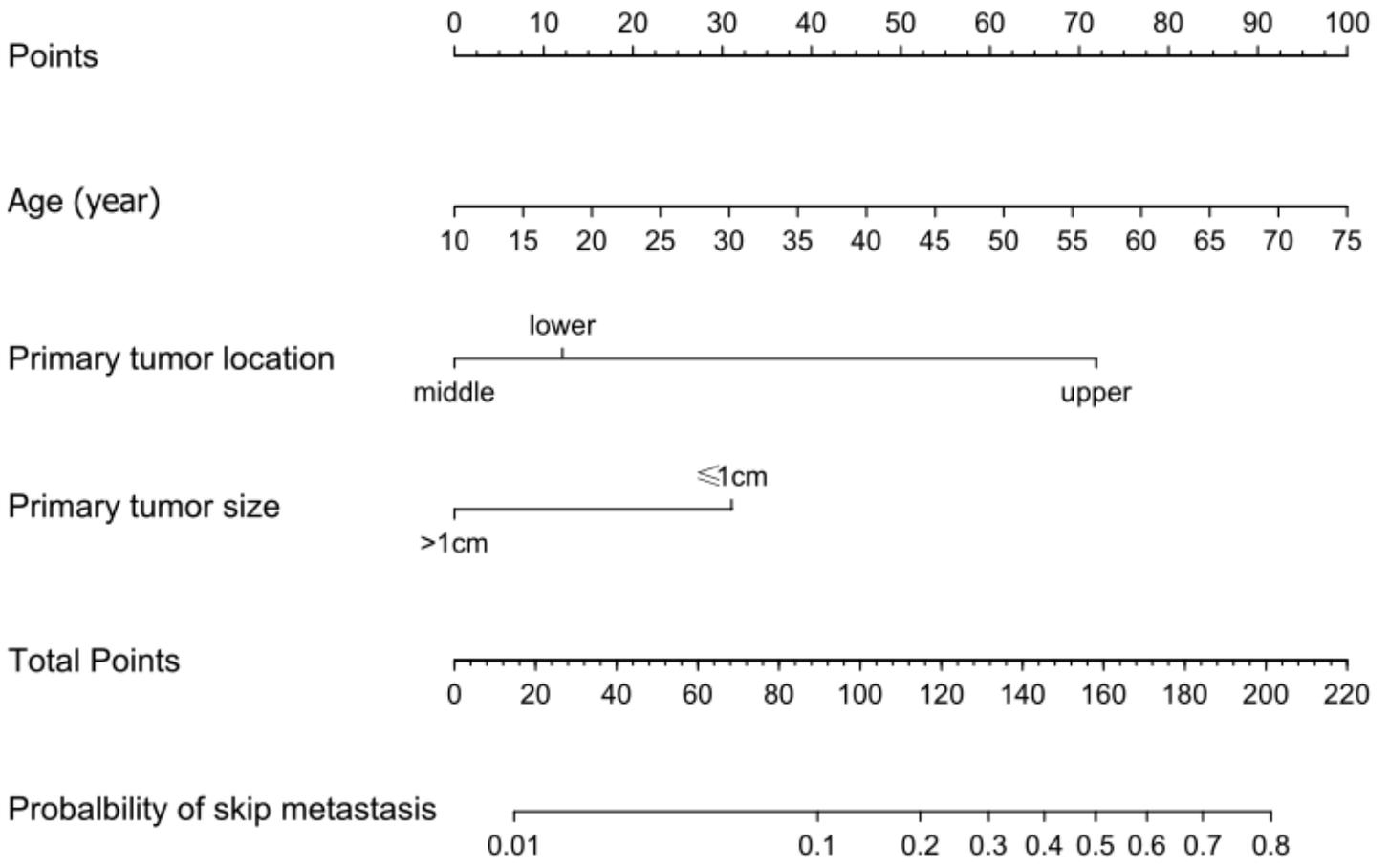
The authors declare that they have no competing interests.

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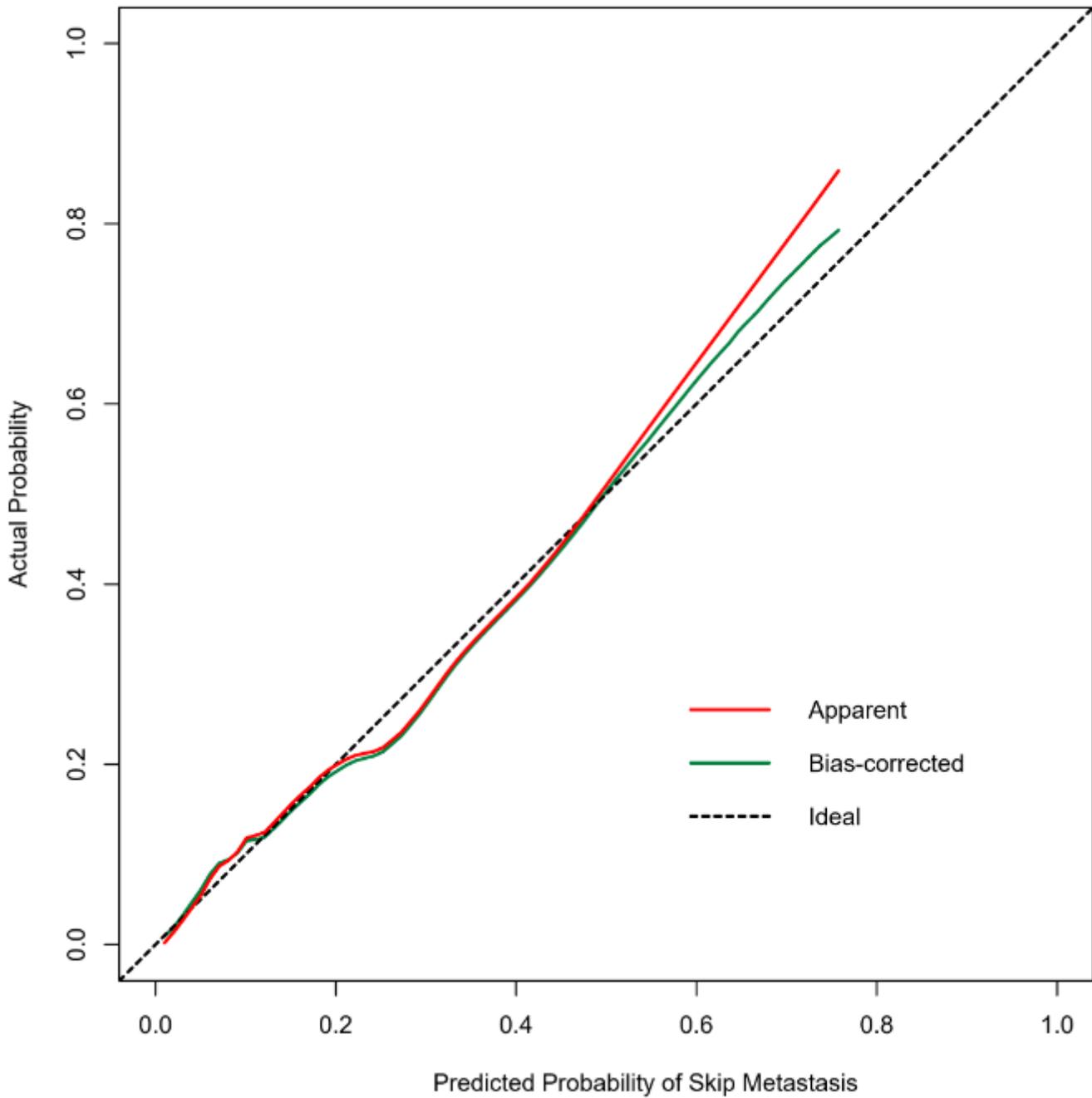
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## Figures



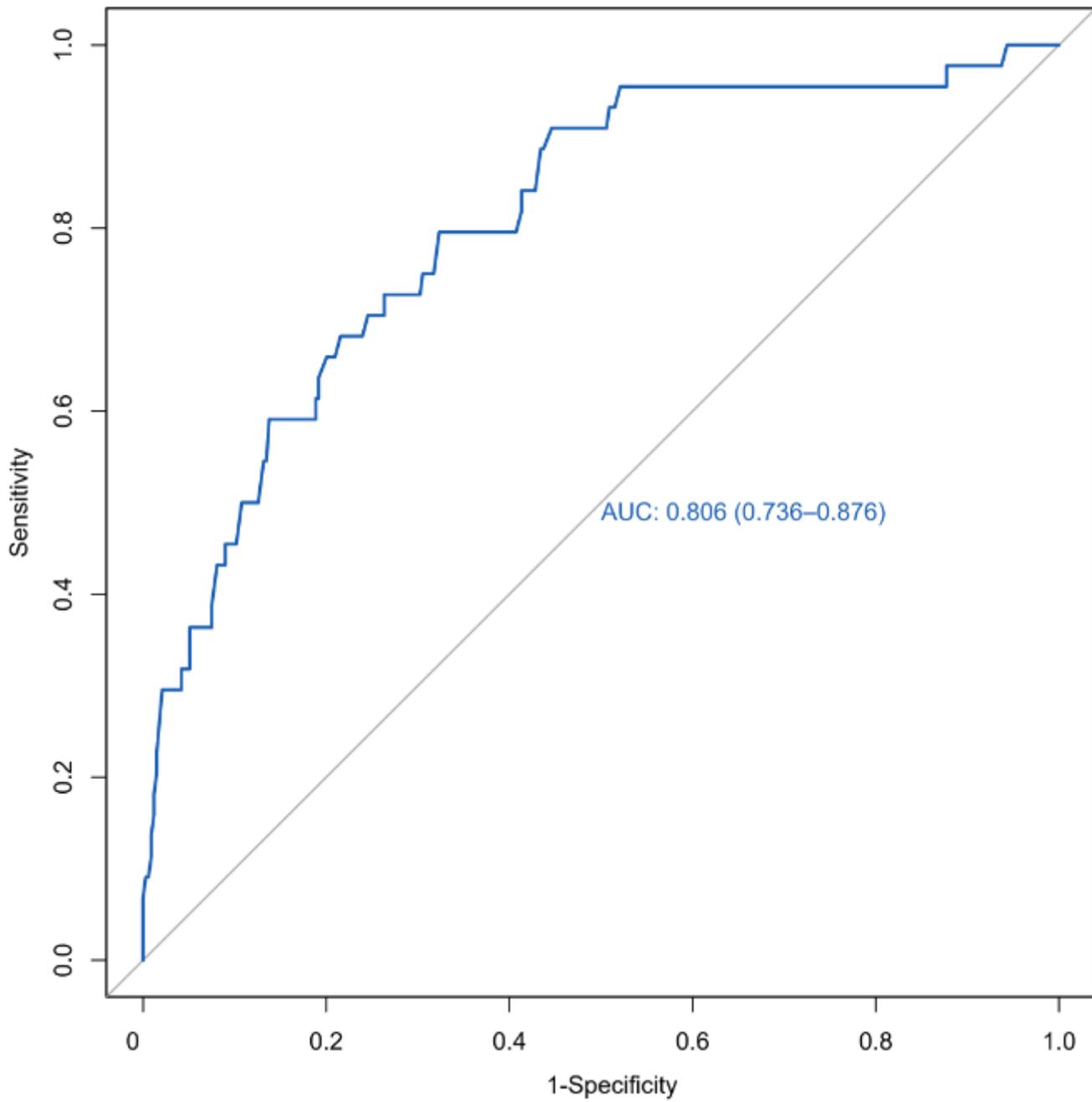
**Figure 1**

Nomogram predicting the probability of skip metastasis.



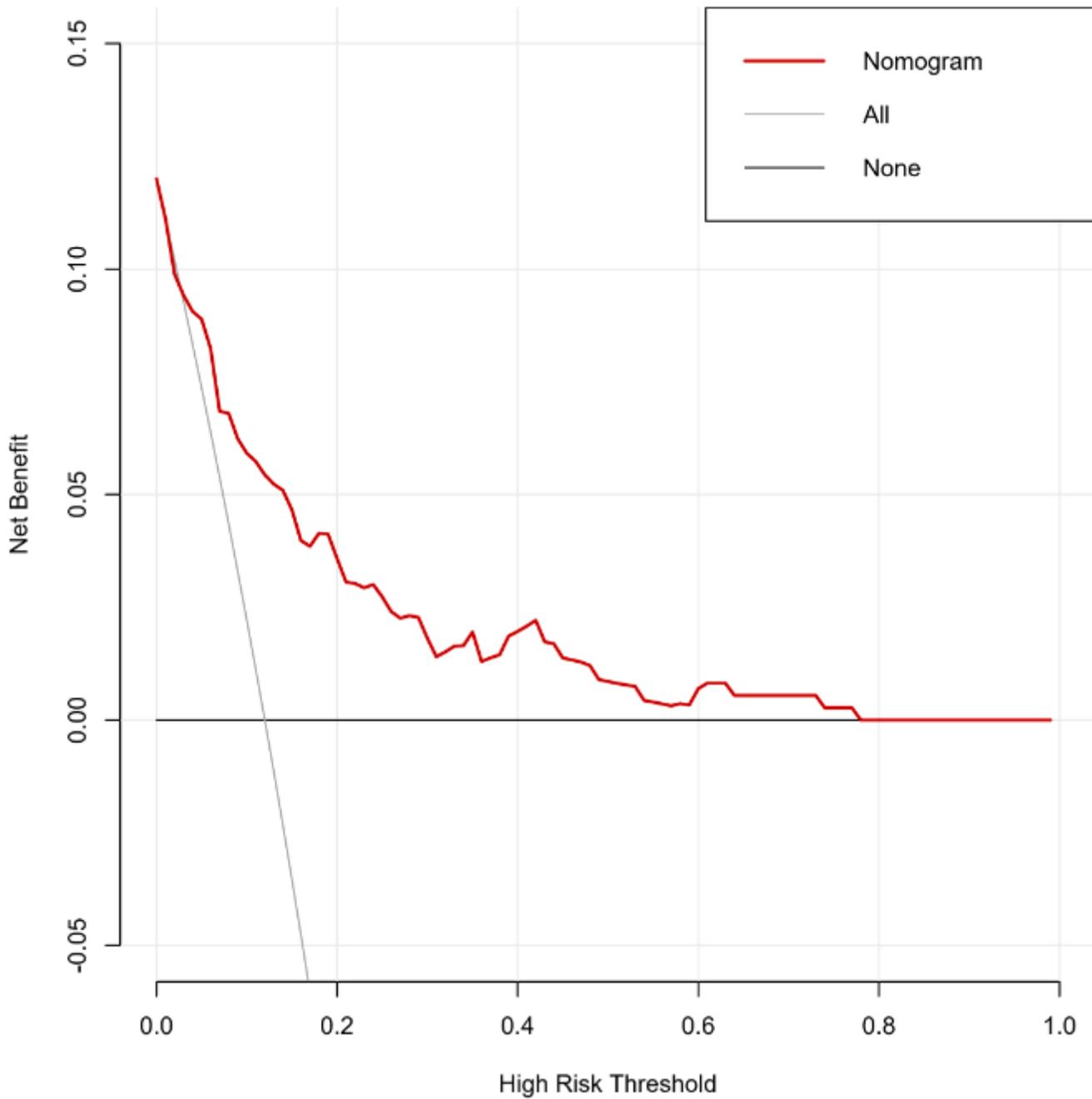
**Figure 2**

Calibration curves of the nomogram for the probability of skip metastasis. On the calibration, the y-axis represents the actual probability, the x-axis represents the nomogram-predicted probability of skip metastasis. The dotted black line is the ideal curve, the blue line represents the bias-corrected curve and the red line represents the nomogram.



**Figure 3**

The ROC curve of nomograms for skip metastasis. The area under the ROC curve (AUC) is 0.806, 95%CI: 0.736-0.876. ROC: Receiver operating characteristic; AUC: Area under curve.



**Figure 4**

Decision curve analysis for nomogram. The black line represents the hypothesis that all PTC patients do not have skip metastasis. The gray line represents the hypothesis that all patients with PTC present skip metastasis. The red line represents the nomogram. The y-axis represents net benefit, and the x-axis represents threshold probability.