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Development and validation of risk prediction models for permanent hypocalcemia after total thyroidectomy in patients with papillary thyroid carcinoma

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Hypocalcemia is a common complication and can be permanent in patients following total thyroidectomy (TT). The aim of this study was to identify factors associated with permanent hypocalcemia and to develop a validated risk prediction model for permanent hypocalcemia to assist surgeons in the appropriate follow-up of high-risk patients regarding supplemental therapy. We included data of 92 patients with papillary thyroid carcinoma (PTC) undergoing TT who were randomly allocated in a 7:3 ratio to a training set ($n = 65$) and validation set ($n = 27$). Univariate and multivariate logistic regression analyses revealed significant correlations of permanent hypocalcemia with parathyroid hormone (PTH) at postoperative month 1 (IM PTH), IM calcium (Ca), and IM phosphorus (P). These variables were constructed two models. Model 1 used the three indicators listed above; model 2 also included tumor, node, metastasis staging. The receiver operating characteristic (ROC) curve analysis showed that the areas under the curve (AUC) for models 1 and 2 were high for both the training set (0.905/0.913) and the validation set (0.894/0.800). Calibration curves showed good agreement between the incidence of permanent hypocalcemia estimated using the predictive models and the actual incidence. Model 1 may be more concise and convenient for clinical use.

Keywords Predictive model, Nomogram, Papillary thyroid carcinoma, Total thyroidectomy, Hypocalcemia

With the increasing popularity of neck ultrasound, the detection and incidence of thyroid cancer is gradually increasing. According to the World Health Organization (WHO) International Agency for Research on Cancer, the incidence of thyroid cancer is the ninth highest in the world, and it is more common in women, at approximately 75%. The median age of patients with thyroid cancer is approximately 50 years, but thyroid cancer is also the most common malignant tumor in people aged 16 to 33 years. PTC accounts for approximately 80% of patients with thyroid malignancy. Surgery remains the primary treatment option for patients with a high suspicion and confirmed PTC by puncture cytology, and TT is the preferred treatment option for non-low risk patients[1]. As with other surgical procedures, patients undergoing TT may experience postoperative complications. Of these, hypocalcemia has a considerable impact on patients' quality of life(QOL) in the postoperative period[2,3]. In 2016, the American Thyroid Association defined hypocalcemia following TT as transient if occurring within 6 months of surgery and permanent if lasting for 6 months or longer postoperatively. Hypoparathyroidism (HPT) is defined as hypocalcemia and inadequate PTH levels, and is diagnosed as a permanent HPT if it persists for 6 or more months after surgery[4]. Most current research on permanent hypocalcemia and HPT recognizes 6 months postoperatively as the time point when the greatest changes occur[5–10]. Hypocalcemia can cause a number of adverse reactions in patients, including muscle twitching, cramps, tingling and numbness, as well as spasms of the facial muscles and wrists. In severe cases, hypocalcemia may induce epilepsy or even cardiac arrhythmias. It is also possible for patients with hypocalcemia to present with no obvious symptoms, although this may be associated with the development of adverse psychiatric symptoms[11]. The early detection of postoperative

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hypocalcemia and prediction of permanent hypocalcemia are of great importance to clinicians. Moreover, timely intervention will minimize the adverse effects on patients[2].

Nomograms are a common tool for assessing the prognosis of oncological diseases[12,13]. A nomogram is a pictorial representation of a complex mathematical formula. Nomograms use biological and clinical variables to graphically depict a statistical prognostic model that generates a probability of a clinical event for a given individual[14,15]. Also, nomograms can be used to predict the risk of postoperative complications[16,17]. In the context of hypocalcemia following TT, most previous studies have concentrated on the examination of risk factors and their predictive value. However, there have been few attempts to develop risk prediction models for the screening of patients at high risk of developing permanent hypocalcemia after TT. The aim of this study was to identify factors associated with permanent hypocalcemia and their follow-up after TT and incorporate these into a nomogram constructed based on a model for predicting permanent postoperative hypocalcemia.

Patients and methods

Study population

In total, 106 patients with malignant thyroid tumors who underwent TT between August 2021 and March 2023 were retrospectively identified in a search of the electronic medical records at Benxi Central Hospital of China Medical University. After 14 exclusions (one patient each with follicular thyroid carcinoma, medullary thyroid carcinoma, preoperative hypocalcemia, and combined hyperthyroidism; four patients with other diseases affecting postoperative Ca in the serum ; and six patients who were lost to follow-up after surgery), data for 92 patients with PTC were included in the statistical analysis.

Surgical procedures

All patients underwent open surgery performed by the same surgical team using an anterior cervical approach with an ultrasonic scalpel. According to the Chinese and American guidelines for the diagnosis and treatment of differentiated thyroid cancer, TT includes central lymph node dissection (CLND) on at least one side of the thyroid gland with the upper border reaching the hyoid bone, the lower border flat on the plane of the innominate artery, the common carotid artery on the outer border, the more superficial deep cervical fascia on the anterior border, and the deeper deep cervical fascia on the posterior border. Bilateral central lymph node dissection (BCLND) was applied in 72 cases. Prophylactic ipsilateral CLND was performed in patients with T1 stage only and biopsy-proven lymph node-negative disease. In our cohort, this approach was applied in 8 cases. Lateral cervical lymph node dissection (LCLND) was performed if the lateral cervical region showed evidence of biopsy-proven metastatic lateral cervical lymphadenopathy. In our cohort, this approach was applied in 12 cases. The lateral cervical region was routinely dissected in zones II to V, up to the digastric muscle, down to the superior margin of the clavicle, inward to the medial border of the carotid sheath, and outward to the anterior border of the trapezius muscle[18,19].

Eligibility criteria

The following inclusion criteria were applied: TT for the first time and postoperative pathological confirmation of PTC; pathology corresponding to the American Joint Committee on Cancer tumor, node, metastasis (TNM) stage; preoperative serum PTH, Ca, P, and magnesium (Mg) levels recorded and rechecked during follow-up at the same hospital; and complete medical and surgical records. Patients with any of the following were excluded: hepatic or renal insufficiency; hyperthyroidism and/or toxic diffuse goiter; preoperative parathyroid or other endocrine disorder; pregnancy and/or lactation; important follow-up data missing; or a disorder of Ca, P, or Mg metabolism before surgery or during follow-up.

Indicators and definitions

The general data collected from patients included information on their age, sex, height, weight, and whether they had any underlying comorbidities associated with Hashimoto's thyroiditis (HT). Additionally, the surgical procedure and pathological staging were documented. Laboratory investigation data encompassed the patients' preoperative Ca, P, Mg, and PTH levels (formulated as the Pre + index), postoperative day 1 (PODI)(formulated as the PODI + index), and postoperative Ca, P, Mg, and PTH levels at 1, 3, and 6 months postoperatively. All blood samples were taken in the morning after an overnight fast.

Defining indicators were as follows: change in PTH=(Pre PTH – PODI PTH)/Pre PTH0; change in serum Ca=(Pre Ca – PODI Ca)/Ca0; change in serum Mg=(Pre Mg – PODI Mg)/Pre Mg0; change in serum P=(PODI P – Pre P)/Pre P0.

Study groups

Included patients were divided into a permanent hypocalcemia group and a non-hypocalcemia group based on a serum Ca threshold of 2.10 mmol/L at 6 months postoperatively.

Statistical analysis

Measurements are expressed as mean ± standard deviation. Counts are expressed as number (percentage). The data were randomly divided into a training set ($n = 65$) and a validation set ($n = 27$) according to a 7:3 ratio. Column line plots were used to illustrate the risk of permanent hypocalcemia in patients following TT. Multivariate logistic regression analyses were conducted to develop and validate the models. Initially, all data from the training and validation sets were analyzed to ascertain whether there was a statistically significant difference between the two sets. This was followed by an analysis of the training sets using univariate logistic regression to identify predictors of permanent hypocalcemia in patients following TT. Finally, the selected predictors were included in multifactorial logistic regression analyses and incorporated into nomograms. The

predictive models were validated using discrimination, accuracy, and clinical validity. In this study, ROC curve analysis showed that AUC could be used to determine the discriminative power of the model.Calibration curves were used to determine the degree of agreement between predicted probabilities and observed outcomes. To assess the clinical validity of the model, decision curve analysis (DCA) was applied. The "pROC" package in R was used to plot ROC curves and the "RMDA" package was used to plot DCA curves. The "RMS" package was used to plot calibration curves and nomograms. All data analyses were conducted using R software version 4.3.0 (The R Project for Statistical Computing, Vienna, Austria), and P-values < 0.05 were considered statistically significant.

Results

Participant characteristics

The baseline characteristics of all patients as well as patients in the training and validation sets were assessed, and the training and validation sets were analyzed. No significant discrepancies were observed in the data between the training set and validation set (Table 1).

Results of univariate and multivariate analyses

Univariate and multivariate logistic regression analyses were performed to identify risk factors for permanent hypocalcemia in 65 patients after TT. The parameters for which $P < 0.20$ was calculated in univariate logistic regression analysis (PODI PTH, PODI Ca, PODI P, PTH change, Ca change, P change, postoperative month 1 [IM] PTH, IM Ca, IM Mg, IM P, postoperative month 3 [IIIM] PTH, IIIMCa and T stage) were included in multivariate logistic regression analysis. The results of this analysis identified IM PTH, IM Ca, and IM P ($P < 0.05$) as independent risk factors for permanent hypocalcemia in patients with PTC after TT (Table 2).

Predictive model development

The prediction model comprised variables with P values < 0.05 in multivariate logistic regression, which were IM PTH, IM Ca and IM P. Predictive model 1 was presented using a nomogram that can be used to quantitatively predict the risk of permanent hypocalcemia in patients after TT. Model 1 was as follows: Logit (p) = 11.9478 − 0.0556×IM PTH − 8.3677×IM Ca + 7.3355×IM P. Model 2 builds on this by incorporating pathological staging and investigating the effect of pathological staging on the predictive model. Model 2 was as follows: Logit (p) = 9.0389 − 0.0556×IM PTH − 6.8710×IM Ca + 6.9819×IM P + 0.7505×TIb + 6.7132×TII + 0.1513×TIIIb − 7.1288×TIVa − 0.5418×NIa − 7.3310×NIb. To increase the usefulness of these models, we generated nomograms showing scores that correspond to each risk factor and a total of all risk factors, corresponding to the risk of permanent hypocalcemia (Figs. 1 and 2).

The application of the nomograms was as follows. According to the figures, the score value corresponding to each prediction index was found and recorded as the total score. The prediction probability corresponding to the total score in the last row of the figure is the risk of permanent hypocalcemia (range 0–1).

Predictive model validation

Discrimination

AUC values of the ROC curves were calculated to assess the discrimination of the predictive model by examining the occurrence of permanent hypocalcemia in patients following TT in the training and validation sets of model 1 and 2. As shown in Fig. 3A,B, the predictive model 1 yielded an AUC value of 0.905 (95% CI = 0.828–0.982), with a specificity of 0.914, and sensitivity of 0.767 in the training set, and an AUC = 0.894 (95% CI = 0.777–1.000), with a specificity of 0.706 and sensitivity of 1.00 in the validation set. Predictive model 2 had an AUC value of 0.913 (95% CI = 0.844–0.982), with a specificity of 0.886 and sensitivity of 0.800 in the training set, and AUC = 0.800 (95% CI = 0.630–0.970), with a specificity of 0.706 and sensitivity of 0.900 in the validation set (Fig. 4A,B). These data indicated that the two nomograms have good discriminatory ability and predictive value and can correctly identify patients at risk of permanent hypocalcemia.

Delong test results

The Delong test was used to determine statistically significant differences in the ROC curves. The Delong test was used for the validation set of models 1 and 2 (Z = 1.199, 95% confidence interval [CI] = − 0.060–0.248, $P = 0.231$). The result showed no statistically significant differences between the two ROC curves and the AUC. Model 2 included TNM staging, indicating that whether the model includes TNM staging makes little difference to the predictive value. Thus, model 1 was found to be more concise than model 2, which is more conducive to clinical application.

Calibration of the predictive models

We constructed calibration curves for the models. The curves for models 1 and 2 in the training set showed that the curve performed well with an additional 1000 bootstraps but performed slightly worse in the validation set (Figs. 5A,B and 6A,B).

Evaluation of clinical validity

The clinical validity of the model was evaluated using DCA; the results are shown in Figs. 7A,B and 8A,B. According to DCA, the net benefits of the predictive models were significantly higher than those of the two extremes. Thus, it could be concluded that the prediction models were clinically effective.

Variables	Total *n* = 92	Training set *n* = 65	Validation set *n* = 27	*P*-Value
Permanent hypocalcemia (%)	40(43.5%)	30(46.2%)	10(37.0%)	0.567
Age (years)	49.80 ± 9.88	48.80 ± 9.99	52.15 ± 9.37	0.132
Gender				0.447
Female (%)	72(78.3%)	49(75.4%)	23(85.2%)	
Male (%)	20(21.7%)	16(24.6%)	4(14.8%)	
Height (cm)	163.89 ± 7.67	164.18 ± 8.02	163.19 ± 6.85	0.688
Weight (kg)	68.41 ± 12.62	69.32 ± 13.72	66.22 ± 9.34	0.216
BMI (kg/ m^2)	25.36 ± 3.61	25.56 ± 3.74	24.88 ± 3.29	0.391
HT (%)	29(33.8%)	22(33.8%)	7 (25.9%)	0.618
Pre PTH (pg/mL)	63.66 ± 21.58	61.83 ± 18.74	68.05 ± 27.13	0.425
Pre Ca (mmol/L)	2.29 ± 0.10	2.29 ± 0.11	2.29 ± 0.10	0.817
Pre Mg (mmol/L)	0.92 ± 0.07	0.91 ± 0.07	0.94 ± 0.07	0.091
Pre P (mmol/L)	1.17 ± 0.18	1.19 ± 0.19	1.13 ± 0.14	0.315
PODI PTH (pg/mL)	22.90 ± 17.34	21.68 ± 17.18	25.84 ± 17.7	0.245
PODI Ca (mmol/L)	2.05 ± 0.16	2.05 ± 0.15	2.06 ± 0.19	0.955
PODI Mg (mmol/L)	0.82 ± 0.07	0.81 ± 0.07	0.83 ± 0.08	0.251
PODI P (mmol/L)	1.32 ± 0.25	1.32 ± 0.25	1.32 ± 0.27	0.784
PTH change	0.64 ± 0.26	0.65 ± 0.25	0.59 ± 0.29	0.443
Ca change	0.10 ± 0.07	0.10 ± 0.07	0.1 ± 0.09	0.859
Mg change	0.11 ± 0.08	0.11 ± 0.08	0.11 ± 0.08	0.849
P change	0.04 ± 0.29	0.03 ± 0.26	0.05 ± 0.35	0.786
IM PTH (pg/mL)	51.69 ± 20.97	49.27 ± 19.76	57.51 ± 22.96	0.110
IM Ca (mmol/L)	2.18 ± 0.18	2.18 ± 0.19	2.21 ± 0.16	0.461
IM Mg (mmol/L)	0.90 ± 0.07	0.91 ± 0.08	0.9 ± 0.06	0.458
IM P (mmol/L)	1.26 ± 0.20	1.26 ± 0.20	1.24 ± 0.21	0.722
IIIM PTH(pg/mL)	54.94 ± 37.49	53.76 ± 41.17	57.77 ± 27.09	0.233
IIIM Ca(mmol/L)	2.17 ± 0.16	2.16 ± 0.16	2.20 ± 0.16	0.352
IIIM Mg (mmol/L)	0.90 ± 0.06	0.89 ± 0.06	0.90 ± 0.06	0.478
IIIM P (mmol/L)	1.23 ± 0.27	1.23 ± 0.29	1.22 ± 0.23	0.767
VIM PTH (pg/mL)	46.94 ± 19.92	45.75 ± 18.75	49.82 ± 22.63	0.414
VIM Ca (mmol/L)	2.13 ± 0.18	2.12 ± 0.18	2.14 ± 0.18	0.352
VIM Mg (mmol/L)	0.89 ± 0.07	0.89 ± 0.07	0.89 ± 0.07	0.867
VIM P (mmol/L)	1.17 ± 0.21	1.17 ± 0.21	1.17 ± 0.20	0.938
Surgical procedure				0.307
BCLND (%)	72(78.3%)	53(81.5%)	19(70.4%)	
Left CLND (%)	3(3.3%)	3(4.6%)	0(0%)	
Right CLND (%)	5(5.4%)	3(4.6%)	2(7.4%)	
BCLND + Left LCLND (%)	7(7.6%)	3(4.6%)	4(14.8%)	
BCLND + Right LCLND (%)	5(5.4%)	3(4.6%)	2(7.4%)	
Pathological staging				
T				0.288
TIa (%)	58(63.1%)	41(63.1%)	17(63%)	
TIb (%)	23(25.0%)	18(27.7%)	5(18.5%)	
TII (%)	4(4.3%)	1(1.5%)	3(11.1%)	
TIIIb (%)	6(6.5%)	4(6.2%)	2(7.4%)	
Continued				
TIVa (%)	1(1.1%)	1(1.5%)	0(0%)	

Variables	Total	Training set	Validation set	
	n = 92	*n* = 65	*n* = 27	*P*-Value
N				0.412
N0 (%)	65(70.7%)	45(69.2%)	20(74.1%)	
NIa (%)	23(25.0%)	18(27.7%)	5(18.5%)	
NIb (%)	4(4.3%)	2(3.1%)	2(7.4%)	
M0 (%)	92(100%)	65(100%)	27(100%)	-

Table 1. Comparison between variables in the training and validation sets. $P < 0.05$ indicates statistical significance. *BMI* body mass index, *HT* Hashimoto's thyroiditis, *PTH* parathyroid hormone, *PODI* postoperative day 1, *Ca* calcium, *Mg* magnesium, *P* potassium, *CLND* central lymph node dissection, *LCLND* lateral cervical lymph node dissection, *T* tumor, *N* node, *M* metastasis, *IM* postoperative month 1, *IIIM* postoperative month 3, *VIM* postoperative month 6, *BCLND* bilateral cervical lymph node dissection.

Discussion

HPT is the most common complication following TT. Biochemical HPT is defined as a low intact PTH level, below the lower limit of the laboratory standard, accompanied by hypocalcemia. Hypocalcemia is a total serum Ca level less than the lower limit of the center-specific reference range[7,11,20]. Hypocalcemia has the potential to cause adverse effects on both the physiological and psychological well-being of patients. Therefore, it is crucial to identify the risk of developing permanent hypocalcemia in the early postoperative period and during follow-up to implement timely interventions and appropriate psychological treatment and improve the patients' QOL. A number of studies have been conducted by researchers in various countries on the risk factors of postoperative hypocalcemia following TT. The results of these studies indicate that age, sex, serum Mg, vitamin D, HT, and a low postoperative PTH level may be risk factors for postoperative hypocalcemia after TT. However, there is currently no internationally accepted conclusion on this matter. The inconsistent results of previous studies may be attributable to data being obtained in different regions using different criteria, the use of various time points for determination of hypocalcemia, and the fact that some studies have included medullary thyroid carcinoma, follicular thyroid carcinoma, and toxic diffuse goiter. The rich blood supply in the thyroid gland means that patients with diffuse toxic goiter are at increased risk of intraoperative injury to the parathyroid gland, which increases the likelihood of postoperative hypocalcemia[21]. Furthermore, patients with medullary thyroid carcinoma are very likely to have hyperparathyroidism[22], which may lead to removal of the parathyroid glands, again increasing the likelihood of postoperative hypocalcemia. Therefore, all patients included in our study were required to have PTC to avoid any bias resulting from the inclusion of different types of thyroid pathology.

PTH is a peptide hormone synthesized and secreted by the parathyroid glands that mainly acts on target organs, including the bones and kidneys, and is involved in the regulation of Ca and P metabolism. Considering that PTH is the main biochemical indicator used to assess serum Ca levels, it has been widely studied as a risk factor for hypocalcemia after TT[23–25]. Researchers who have mainly focused on the ability of postoperative PTH levels and changes therein to predict hypocalcemia have measured PTH at times ranging from intra-operative skin closure up to 48 h and even up to 4 days postoperatively[24–39]. These studies have suggested that both the percent change and absolute value of PTH levels at 10–20 min and less than 23 h postoperatively can predict the development of hypocalcemia[26–32,36,38]. Additionally, the degree of decrease in PTH levels for a period of 4 h postoperatively is a more accurate predictor of postoperative hypocalcemia following TT than PTH levels alone[31,39], and at 4 versus 23 h postoperatively or even at PODI, there may be no significant difference in PTH levels[30,37]. It has also been demonstrated that combining PODI PTH with PODI Ca levels may result in more reliable outcomes[40,41].

There are inherent difficulties in obtaining 100% long-term follow-up rates after patients are discharged from the hospital following surgery. As a result, data are largely incomplete, making the reported incidence of long-term complications unreliable. The UK Registry of Endocrine and Thyroid Surgeons have demonstrated a lack of data on complementary therapy at 6 months after thyroidectomy in nearly 22% of patients[42]. Therefore, a challenge remains in accurately identifying patients who develop permanent hypocalcemia, and it is important for surgeons to strengthen regular follow-up and detection of all patients after thyroid surgery. Similar to previous research, our univariate logistic regression analyses revealed that permanent hypocalcemia in patients after TT was significantly associated with PODI PTH, PODI Ca, PODI P, PTH change, Ca change and P change. However, we also found that follow-up data such as IM PTH, IM Ca, IM P, IIIM PTH, and IIIM Ca were associated with permanent hypocalcemia. Further multivariate logistic regression analyses also showed that IM PTH, IM Ca, and IM P may be independent risk factors for permanent hypocalcemia.

Disturbances in serum magnesium metabolism may be closely related to postoperative hypocalcemia following TT[43,44]. If PODI Mg is less than 1.8 mg/dL, the patient requires Ca supplementation, suggesting that low Mg may indeed be associated with postoperative hypocalcemia[37]. It has been demonstrated that patients with hypomagnesaemia within 2 days of surgery have a significantly increased risk of developing postoperative temporary or even permanent hypocalcemia[45]. Furthermore, an Mg concentration below 0.78 mmol/L on postoperative day 2 (PODII) has been demonstrated to possess a certain predictive value for postoperative hypocalcemia, with a sensitivity and specificity of 71.2% and 77.5%, respectively[26]. In our study, we did not find a significant relationship between hypocalcemia and Mg levels for preoperative Mg, postoperative Mg and its change. This may be associated with the fact this was a single-center study with a smaller sample size[46]. A limited

Variables	Univariate analyse			Multivariate analyse		
	OR	95% CI	P-Value	OR	95% CI	*P* Value
Age	1.002	0.953–1.053	0.940			
Gender	1.227	0.392–3.857	0.723			
Height (cm)	1.021	0.960–1.088	0.503			
Weight (kg)	0.995	0.959–1.031	0.778			
BMI (kg/ m^2)	0.936	0.814–1.069	0.338			
HT	1.667	0.593–4.778	0.333			
Pre PTH (pg/mL)	1.005	0.978–1.032	0.731			
Pre Ca (mmol/L)	0.061	< 0.001–6.670	0.252			
Pre Mg (mmol/L)	6.718	0.006-9339.537	0.597			
Pre P (mmol/L)	2.124	0.158–31.519	0.569			
PODI PTH (pg/mL)	0.965	0.931–0.996	0.039	0.997	0.827–1.211	0.969
PODI Ca (mmol/L)	0.032	0.001–0.877	0.050	1.345e + 14	8.874-1.643e + 36	0.089
PODI Mg (mmol/L)	2.060	0.002-2529.993	0.838			
PODI P (mmol/L)	4.683	0.610-48.892	0.158	5.311	< 0.001-2.296e + 05	0.737
PTH change	27.342	2.988-347.751	0.006	43.196	0.002-1.90e + 07	0.490
Ca change	146.888	0.094-4.236e + 05	0.195	2.590e + 27	3162.804-4.928e + 67	0.070
Mg change	1.779	0.004-936.644	0.855			
P change	8.010	1.098–75.526	0.051	217.715	0.460-3.222e + 06	0.150
IM PTH (pg/mL)	0.936	0.900-0.967	< 0.001	0.760	0.581–0.895	0.008
IM Ca (mmol/L)	< 0.001	< 0.001–0.012	0.001	3.397e-08	8.512e-17-0.004	0.019
IM Mg (mmol/L)	0.005	< 0.001–3.890	0.130	1.126e + 07	0.139-3.027e + 18	0.123
IM P (mmol/L)	88.497	26.853-69553.910	0.001	1.223e + 07	502.204-1.248e + 15	0.015
IIIM PTH (pg/mL)	0.964	0.936–0.988	0.007	1.022	0.894–1.110	0.740
IIIM Ca (mmol/L)	0.002	2.504e-05-0.069	0.002	0.001	1.356e-09-14.208	0.244
IIIM Mg (mmol/L)	0.419	< 0.001-990.781	0.825			
IIIM P (mmol/L)	2.970	0.501–27.713	0.267			
Surgical procedure						
BCLND	Reference	Reference	Reference			
Left CLND	0.604	0.027–6.681	0.688			
Right CLND	0.604	0.027–6.681	0.688			
BCLND + Left LCLND	2.417	0.219–53.888	0.482			
BCLND + Right LCLND	2.417	0.219–53.888	0.482			
Pathological staging						
T						
TIa	Reference	Reference	Reference	Reference	Reference	Reference
TIb	2.455	0.801–7.962	0.121	4.138	0.091-342.638	0.463
TII	2.446e + 07	1.196e-205-NA	0.994	0.730	2.134e-149-NA	0.100
TIIIb	1.563	0.173–14.117	0.671	0.082	< 0.001–12.176	0.362
TIVa	< 0.001	NA-2.029e + 205	0.854	4.081e-09	NA-1.403e + 140	0.996
N						
N0	Reference	Reference	Reference			
NIa	1.563	0.521–4.811	0.427			
NIb	< 0.001	NA-2.94e + 108	0.788			

Table 2. Univariate and multivariate logistic regression analyses. *BMI* body mass index, *HT* Hashimoto's thyroiditis, *PTH* parathyroid hormone, *PODI* postoperative day 1, *Ca* calcium, *Mg* magnesium, *P* potassium, *CLND* central lymph node dissection, *LCLND* lateral cervical lymph node dissection, *T* tumor, *N* node, *M* metastasis, *IM* postoperative month 1, *IIIM* postoperative month 3, *OR* odds ratio, *CI* confidence interval, *VIM* postoperative month 6, *BCLND* bilateral cervical lymph node dissection.

number of studies have investigated the potential of serum P levels as a predictor of postoperative hypocalcemia following TT. One study demonstrated that in comparison with the preoperative level, a 40% increase in blood P levels on PODII can predict the development of postoperative hypocalcemia on PODII, with an AUC of 0.80 and with sensitivity and specificity of 60.6% and 83.8%, respectively[47]. However, no significant difference between blood P levels and postoperative hypocalcemia was reported in other studies[26,29]. The results of our study indicated that P change and IM P may be associated with the risk of developing permanent hypocalcemia.

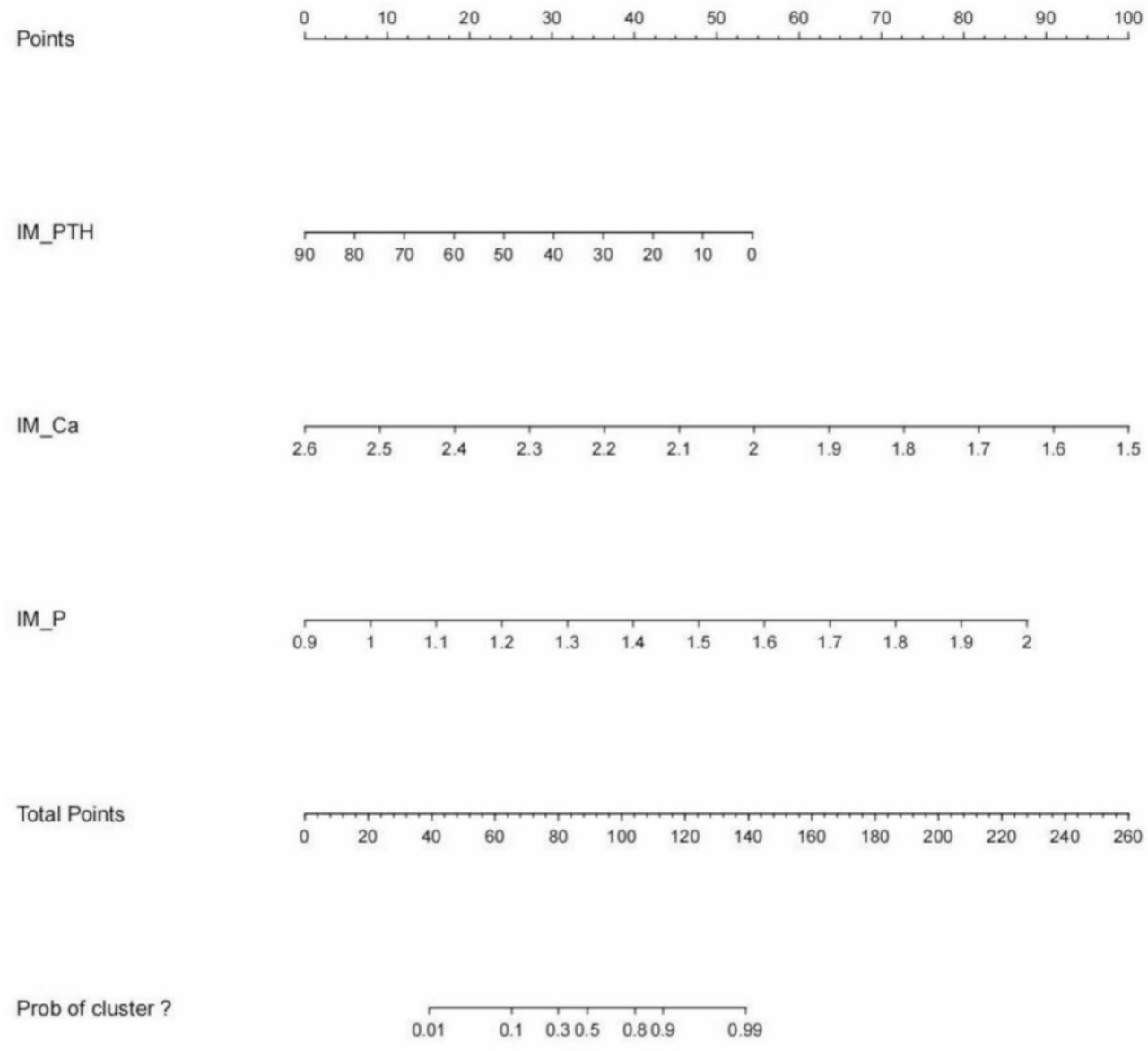


Fig. 1. Model 1 nomogram. *PTH* parathyroid hormone, *Ca* calcium, *P* potassium, *IM* postoperative month 1.

In addition to the above indicators, vitamin D is involved in the regulation of serum Ca[48]. However, the effect of vitamin D on postoperative hypocalcemia is controversial[49,50]. Preoperative vitamin D deficiency may be associated with risk factors for postoperative hypocalcemia[51,52]. The lack of vitamin D monitoring in our study may affect the accuracy of the prediction models owing to financial constraints.

Based on our research, the constructed prediction models took into account the influence of multiple factors on the occurrence of permanent hypocalcemia. Model 1 uses three metrics, IM PTH, IM Ca, and IM P. Model 2 additionally incorporates TNM staging to analyze the potential impact of pathological staging. According to the Delong test, there may not be a significant difference in the predictive value of these two models, and good predictive results can be achieved using model 1 alone, which is more conducive to clinical work. We further verified the consistency between the incidence of permanent postoperative hypocalcemia estimated using the predictive models and its actual incidence. Our study differs from previous studies that have only used independent indicators to predict the risk of developing permanent hypocalcemia. The constructed models can provide guidance and a reference for the follow-up period and key patient indicators that should be monitored after discharge. We also demonstrated the potential value of nomograms for assessing postoperative complications.

Postoperative hypocalcemia not only impacts patients' QOL by causing clinical symptoms but also imposes a psychological burden due to the need for frequent oral calcium supplementation[2,53]. Educating patients on self-management of symptoms and adjustment of calcium supplementation regimens can alleviate some discomfort. However, persistent symptoms and psychological distress may lead to significant frustration and emotional strain[2]. Studies have shown that recombinant human parathyroid hormone (rhPTH) can improve patients' QOL

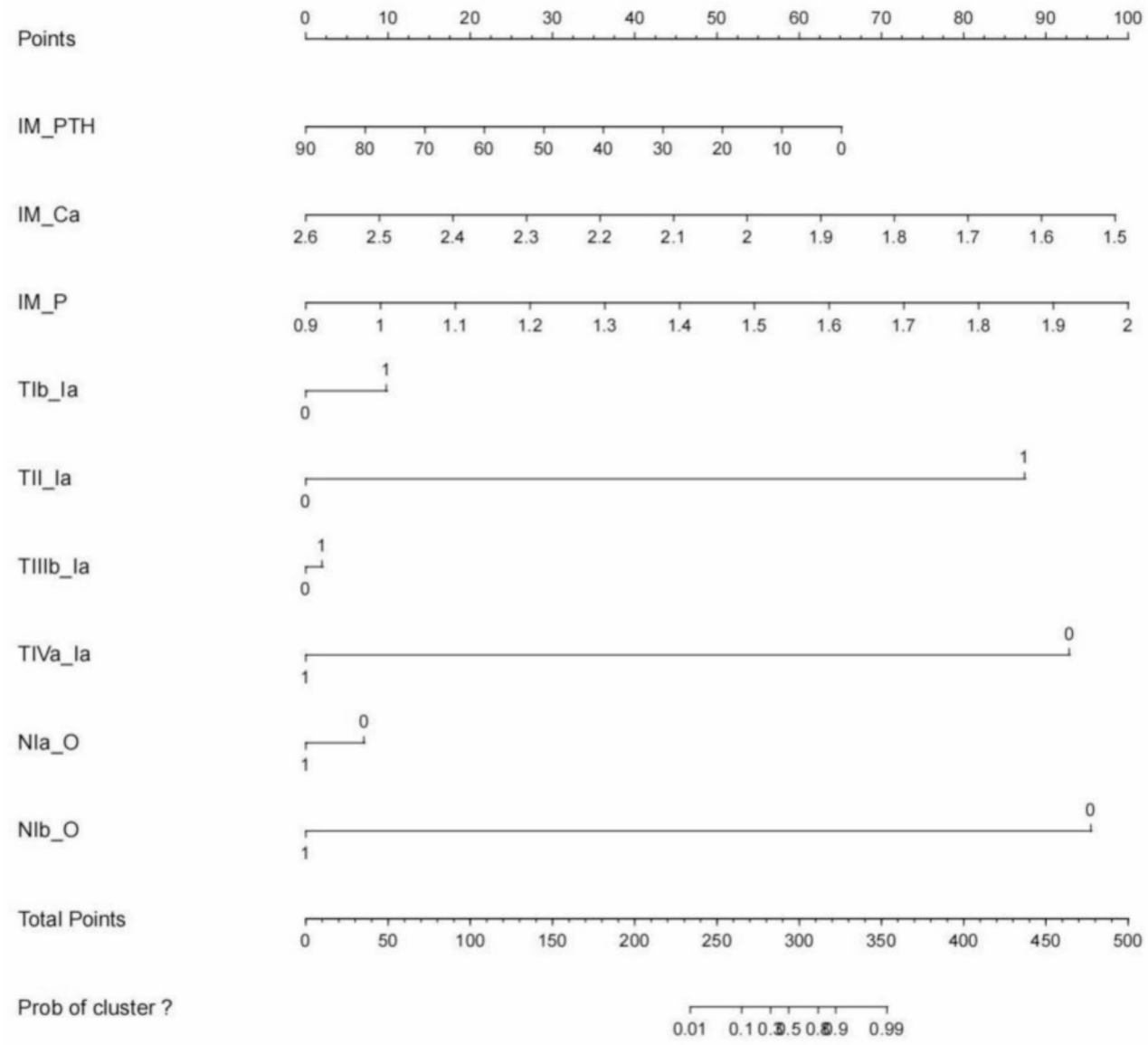


Fig. 2. Model 2 nomogram. *PTH* parathyroid hormone, *Ca* calcium, *P* potassium, *IM* postoperative month 1, *T*, tumor, *N* node.

and reduce the adverse effects associated with prolonged calcium supplementation[54–56]. Our model predicts the risk of permanent hypocalcemia at one month postoperatively, allowing surgeons to involve endocrinologists in patient support groups at an early stage. This collaboration facilitates timely, individualized adjustments to postoperative calcium supplementation and enables prompt evaluation of rhPTH treatment suitability. In summary, the proposed model provides valuable insights during the early postoperative period, ultimately enhancing patients' QOL.

The present study has some limitations. Because this was a single-center retrospective study, the sample size was limited by regional demographic characteristics. Also, the study population mainly included middle-aged and older patients, with few patients in the age group 18–30 years, which may have influenced our results. A lack of assessment of perioperative vitamin D and patients' nutritional status may have introduced bias into our findings. Furthermore, a lack of consensus on the definition of transient and permanent hypocalcemia may also affect the accuracy of the prediction models[10,35,57,58]. Another limitation of our study is the lack of intra-operative measurement of PTH levels. Previous studies have demonstrated that it is associated with postoperative hypocalcaemia and could be used as a real-time indicator for intra-operative decision-making[7]. Including intra-operative PTH data in future studies may help refine predictive models and provide a more comprehensive understanding of factors influencing long-term hypocalcemia outcomes. The lack of an external validation cohort is also a limitation. The inclusion of an external validation cohort would help to validate the generalisability of the model across different populations. Despite the above limitations, we believe that our

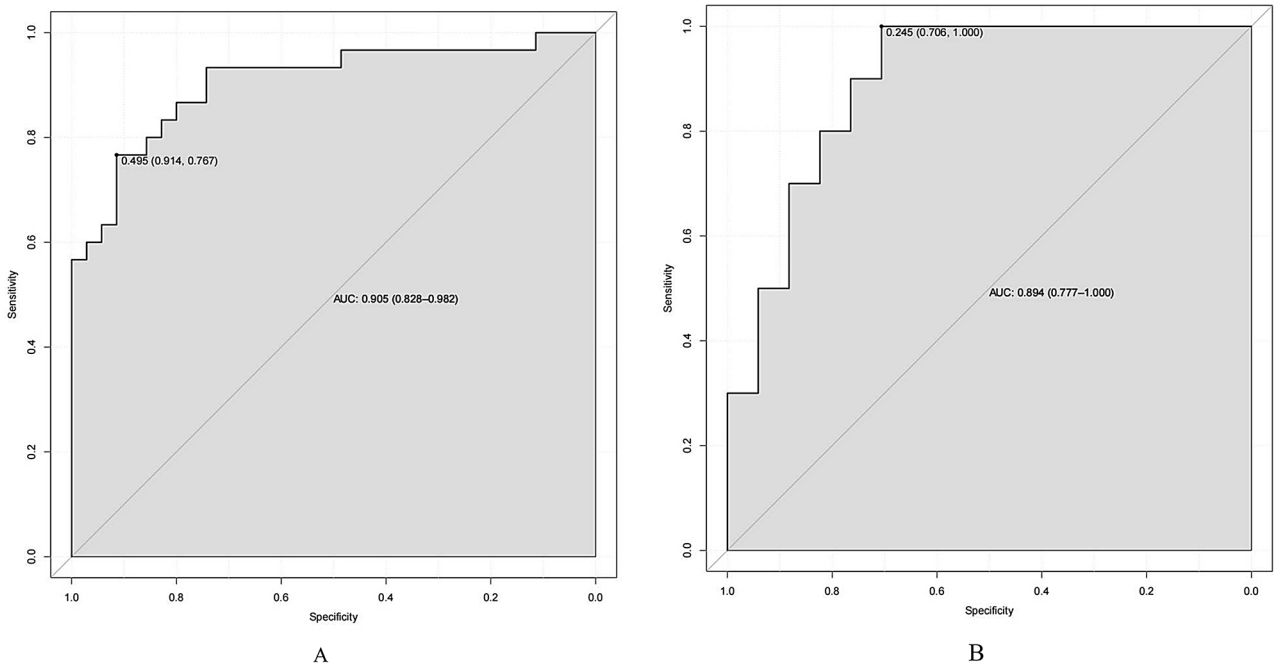
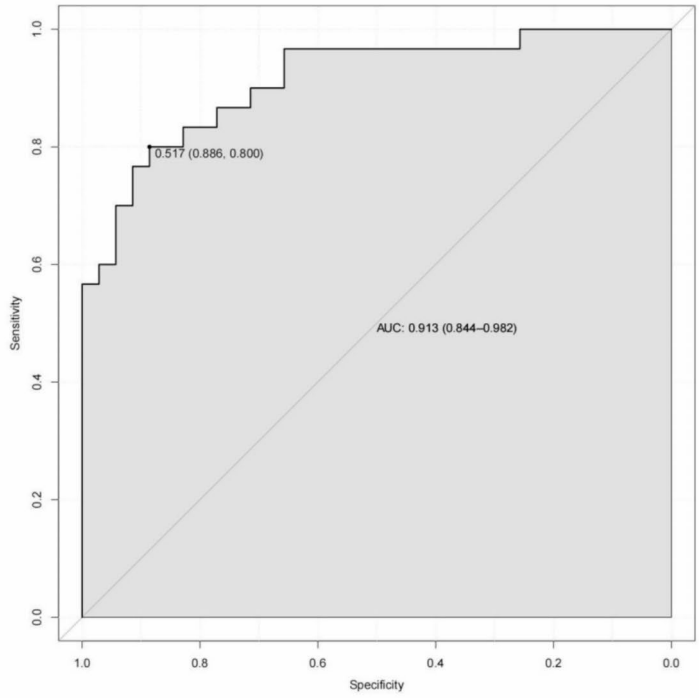


Fig. 3. (**A**) Model 1 nomogram receiver operating characteristic (ROC) curves generated from the training set; (**B**) Model 1 nomogram ROC curves generated using the validation set. AUC, area under the ROC curve.

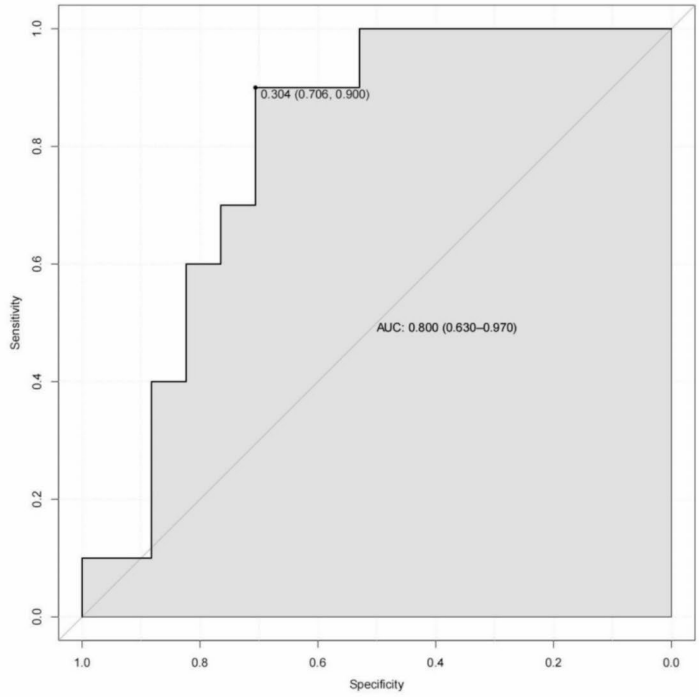
nomograms can be helpful for clinical work. A potential future avenue of research is the conduct of large-scale, multi-center cohort studies, which can enhance the model and facilitate the acquisition of greater external utility.

Conclusions

In this study, we established a nomogram to help clinicians predict the risk of permanent hypocalcemia in patients with PTC following TT. This tool could help clinicians quantify the potential incidence of permanent hypocalcemia. In the future, we will conduct additional multi-center prospective studies to improve the clinical application value of the nomogram.

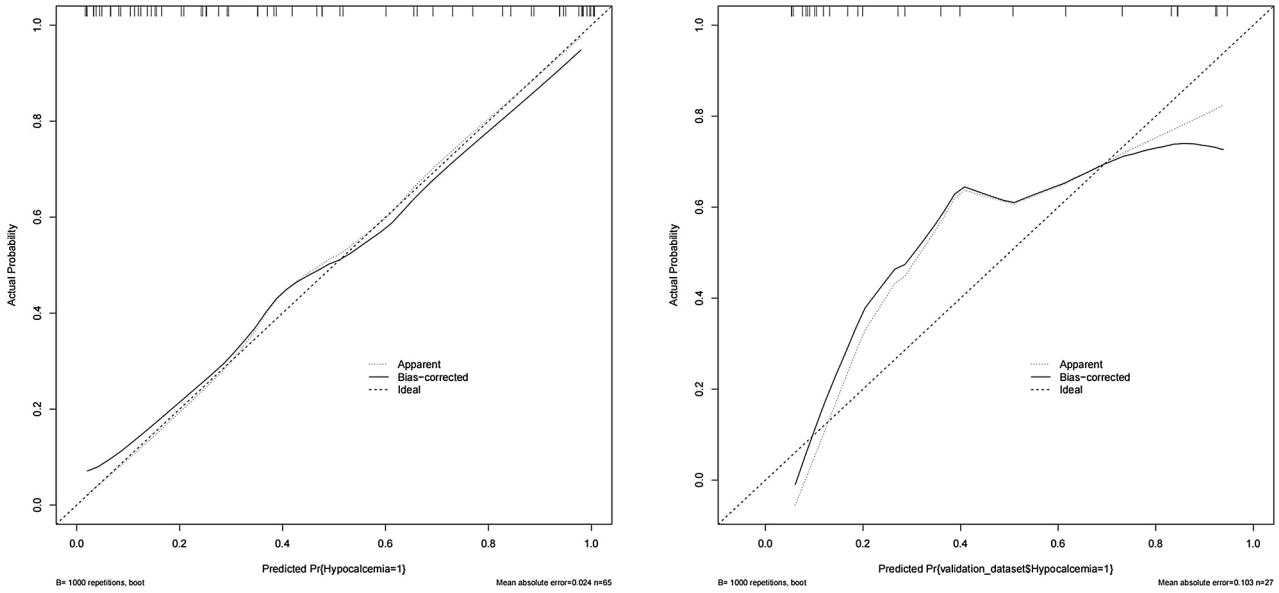


A



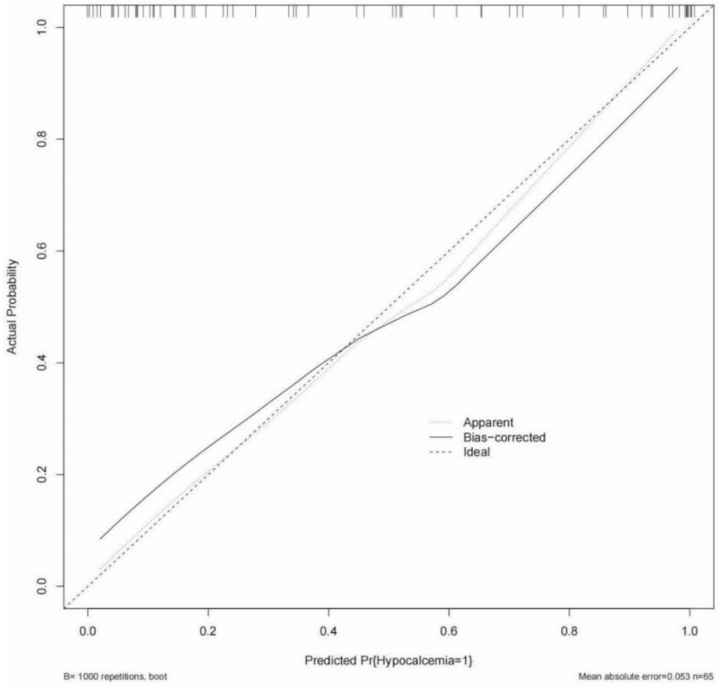
B

Fig. 4. (**A**) Model 2 nomogram receiver operating characteristic (ROC) curves generated from the training set; (**B**) Model 2 nomogram ROC curves generated using the validation set. AUC, area under the ROC curve.

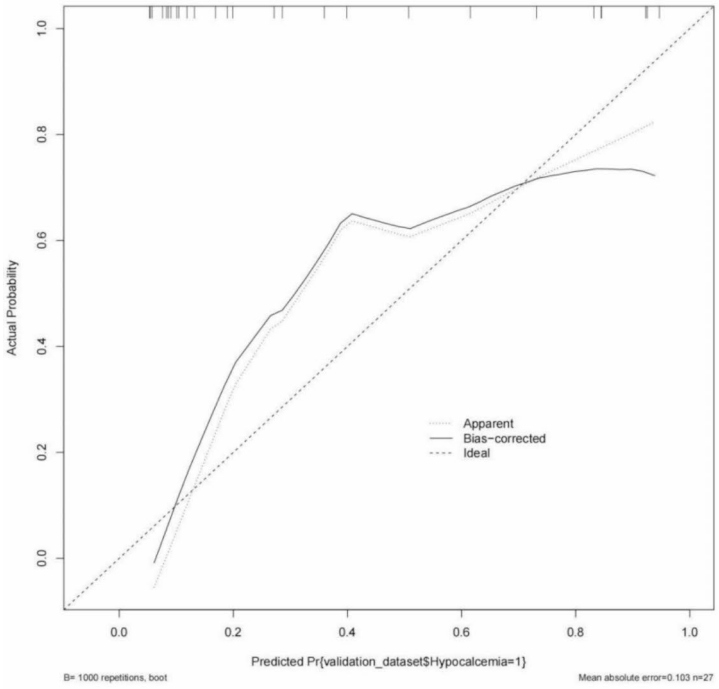


A B

Fig. 5. (**A**) Calibration plot for the training set of Model 1; (**B**) calibration plot for the validation set of Model 1.

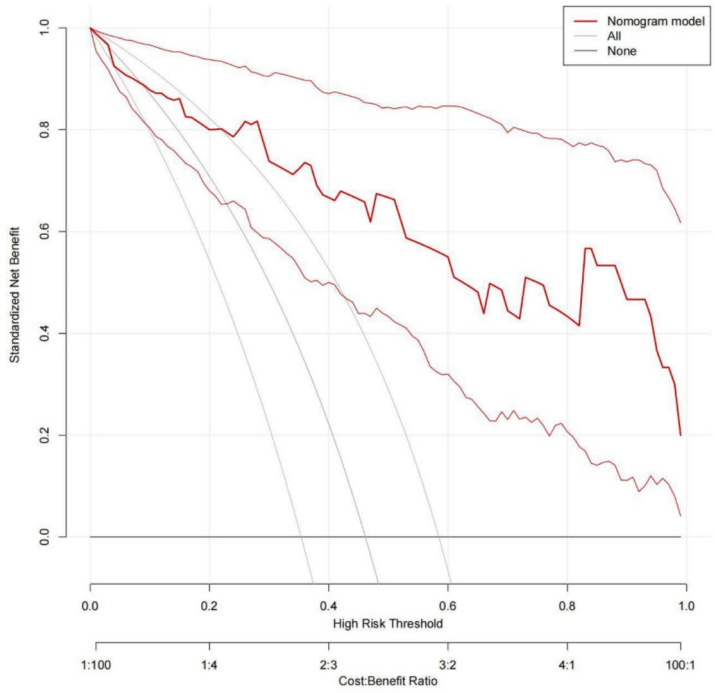


A

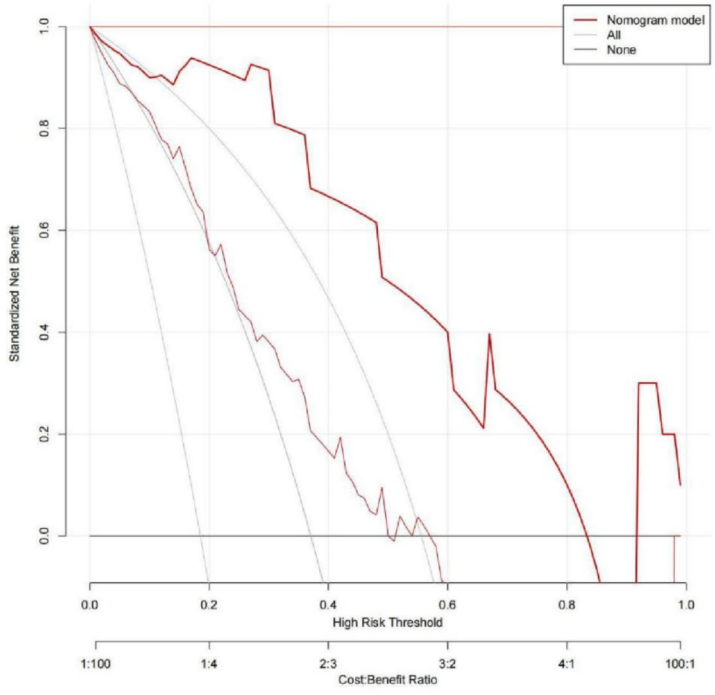


B

Fig. 6. (**A**) Calibration plot for the training set of Model 2; (**B**) calibration plot for the validation set of Model 2.

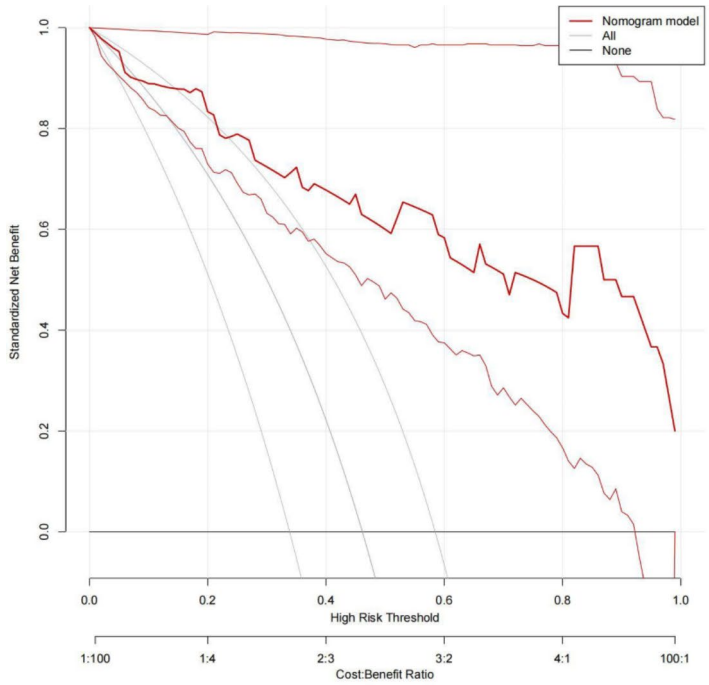


A

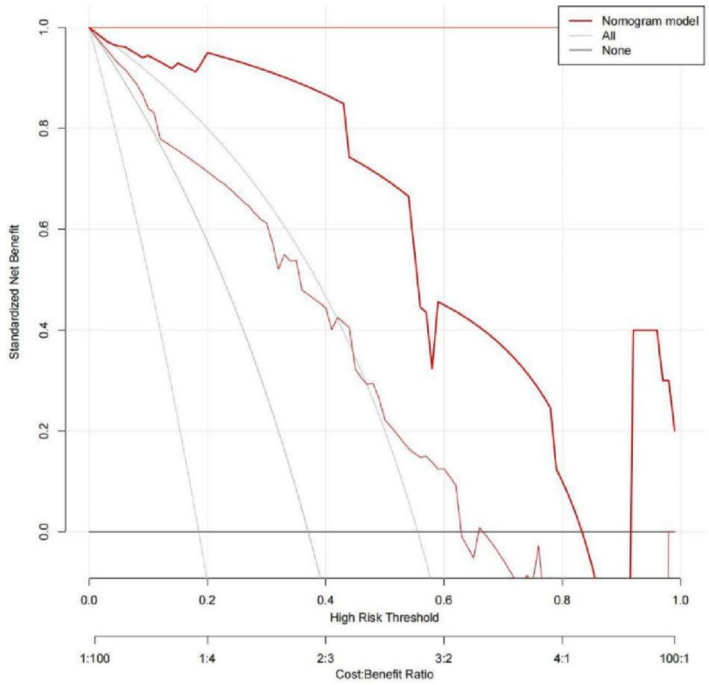


B

Fig. 7. (**A**) Decision curve analysis (DCA) curves for the training set of Model 1 and 95% confidence interval (CI); (**B**) DCA curves for the validation set of Model 1 and 95% CI.



A



B

Fig. 8. (**A**) Decision curve analysis (DCA) curves for the training set of Model 2 and 95% confidence interval (CI); (**B**) DCA curves for the validation set of Model 2 and 95% CI.

Data availability

The data used in this study can be made available upon reasonable request to the corresponding author.

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Author contributions
BHC and YY participated in writing the manuscript and analyzing the data. BHC and XCL participated in the design and conceptualization of the study. CGZ and MMJ approved the fnal version of the manuscript. All authors were involved in revising the manuscript and read and approved the submitted version.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study was approved by the Ethics Committee of Benxi Central Hospital of China Medical University. This study adhered to the tenets of the Declaration of Helsinki. This was a retrospective study, and the data used were obtained from the electronic medical records at the hospital, with patient identifiers removed, so that patient privacy and related data would not be disclosed. The study was approved by the ethics committee of our institution, and informed consent was exempted.

Additional information
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