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Original Article

Analysis of risk factors and development of a risk prediction model for postoperative hypocalcemia in differentiated thyroid cancer

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Abstract: Objective: To systematically analyze the risk factors of hypocalcemia following surgery for differentiated thyroid cancer (DTC), and to develop and validate a high-precision Nomogram-based prediction model, so as to provide a basis for accurate clinical prevention and management. Methods: This retrospective analysis included 597 DTC patients admitted between March 2019 and January 2025 (training set: n=353; validation set: n=133: external validation set: n=111). Patient features (age, sex, body mass index, diabetes history, etc.), surgical factors (thyroidectomy extent, lymph node dissection, etc.), pathological characteristics (capsular invasion, Tumor, Node, Metastasis [TNM] staging, etc.), and postoperative biochemical indicators (intact parathyroid hormone [iPTH] and blood calcium) were collected. Independent risk factors were screened by univariate and multivariate logistic regression. A Nomogram was constructed based on these factors, and its predictive performance was evaluated using the area under the receiver operating characteristic (ROC) curves (AUC), calibration plots, and decision curve analysis (DCA), with comparisons made to postoperative iPTH-based predictions. Results: Multivariate logistic regression identified the following as independent predictors of hypocalcemia: diabetes history (OR=3.132, P=0.006), bilateral thyroidectomy (OR=2.142, P=0.023), lateral compartment lymph node dissection (OR=2.011, P=0.037), capsular invasion (OR=3.196, P<0.001), surgical time (OR=10.843, P<0.001), and intraoperative bleeding (OR=7.493, P<0.001). The Nomogram model exhibited excellent discriminatory ability across the training (AUC=0.888), validation (AUC=0.866), and external validation sets (AUC=0.913). Calibration curves and DCA demonstrated that the Nomogram had high prediction consistency and clinical net benefits (peak net benefits: 56.94%, 62.40%, and 63.90%, respectively). Moreover, the model significantly outperformed iPTH-based predictions in both the training (P=0.019) and external validation cohorts (P=0.042). Conclusions: Diabetes history, bilateral thyroidectomy, lateral lymph node dissection, capsular invasion, prolonged surgical time (≥82.5 min), and increased intraoperative bleeding (≥25.5 mL) are significant risk factors for postoperative hypocalcemia in DTC patients. The Nomogram model, integrating these factors, outperforms iPTH-based predictions and offers a precise tool for preoperative risk assessment and postoperative management to reduce hypocalcemia and improve patient outcomes.

Keywords: Differentiated thyroid cancer, hypocalcemia, risk factors, Nomogram, risk prediction model, parathyroid hormone

Introduction

Differentiated thyroid cancer (DTC), encompassing papillary and follicular thyroid carcinomas, accounts for over 90% of all thyroid malignancies [1, 2]. With advancements in diagnostic imaging and widespread health screenings, the global incidence of DTC has steadily increased [3]. Although DTC typically has a favorable prognoses, with 5-year survival rates exceeding 95%, surgical resection - the mainstay treatment - may lead to complications that impair recovery and diminish quality of life [4]. Among these, hypocalcemia (HC) is one of the most frequent and clinically significant postoperative complications, affecting 20%-50% of patients [5]. HC contributes to prolonged hospitalization, increased healthcare costs, and potentially severe outcomes [6]. Therefore, understanding its risk factors and developing effective predictive tools are of considerable clinical relevance.

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Postoperative HC primarily arises from parathyroid gland injury, resection, or vascular damage during surgery, leading to reduced serum calcium levels. Clinically, it may present with perioral or limb numbness, muscle cramps, tetany, and life-threatening arrhythmia and laryngospasm [7, 8]. Numerous risk factors for HC have been identified. Preoperative vitamin D deficiency significantly increases HC risk [9], while a higher body mass index (BMI ≥25) appears protective. Central compartment lymph node dissection (CCLND) is associated with increased HC incidence [10]. As symptoms can develop within hours to days postoperatively, early identification of at-risk patients and timely intervention - such as parathyroid preservation and calcium/vitamin D supplementation - are critical to minimizing complications and improving outcomes [11].

Surgical extent, especially total thyroidectomy and bilateral CCLND, has been strongly associated with postoperative HC, with a sharp postoperative decline in intact parathyroid hormone (iPTH) levels [12]. Other factors, such as gender, lymph node dissection (LND), and preoperative serum calcium levels, have also shown associations with HC [13]. However, most studies focus on individual or limited risk factors, lacking an integrative approach that includes demographic, surgical, and pathological variables. Moreover, existing HC prediction models are limited in number, often lack external validation, and have limited generalizability across different populations. Reliance on single indicators such as iPTH lacks the predictive precision required for clinical use. For instance, although Mattoo et al. identified early postoperative iPTH as a potential predictor of HC [14], its sensitivity and specificity vary based on timing. Similarly, Lee et al. suggested that the postoperative iPTH decline could predict symptomatic HC [15], but the model's specificity remains suboptimal. Other studies have acknowledged the utility of iPTH for discharge planning, but found it inadequate for comprehensive HC risk assessment [16, 17].

To address these limitations, this study systematically investigated risk factors associated with postoperative HC in patients undergoing DTC surgery and identified independent predictors via multivariate logistic regression. Based on these predictors, a Nomogram prediction model was developed to visually quantify individual risk contributions, enabling preoperative risk stratification and intraoperative decision-making. The model's performance is rigorously evaluated in terms of discrimination, calibration, and clinical applicability using training, validation, and external test sets. Additionally, we compared the model's predictive ability with early postoperative iPTH levels to demonstrate its superiority and generalizability. This integrative, user-friendly model may serve as a practical tool for guiding parathyroid gland protection and postoperative calcium management, ultimately reducing HC incidence and improving patient outcomes.

Methods and materials

Sample size estimation

Based on literature review, the incidence of HC has been reported to range from 36% [15] to 49.19% [6]. Using the formula of $N=Z^2 \times [P \times (1-P)]/E^2$, a cohort of 354-384 cases was calculated to be sufficient for this study.

General data

This retrospective study involved DTC patients treated at the Second Affiliated Hospital of Zunyi Medical University between March 2019 and January 2025. The cohort was further stratified into a training set (353 patients treated from January 2022 to January 2025), a validation set (133 cases from January 2020 to December 2021), and an external validation set (111 subjects from March 2019 to December 2019). The study protocol was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zunyi Medical University (**Figure 1**).

Patient selection criteria

Inclusion criteria: 1. Patients diagnosed with DTC (papillary or follicular thyroid carcinoma) confirmed by pathology to ensure disease-specific consistency [18]; 2. Patients who underwent partial or total thyroidectomy (unilateral or bilateral procedures) during the study period; 3. Complete records of postoperative serum calcium and iPTH levels, enabling the evaluation of HC and related factors; 4. Complete clinical data.

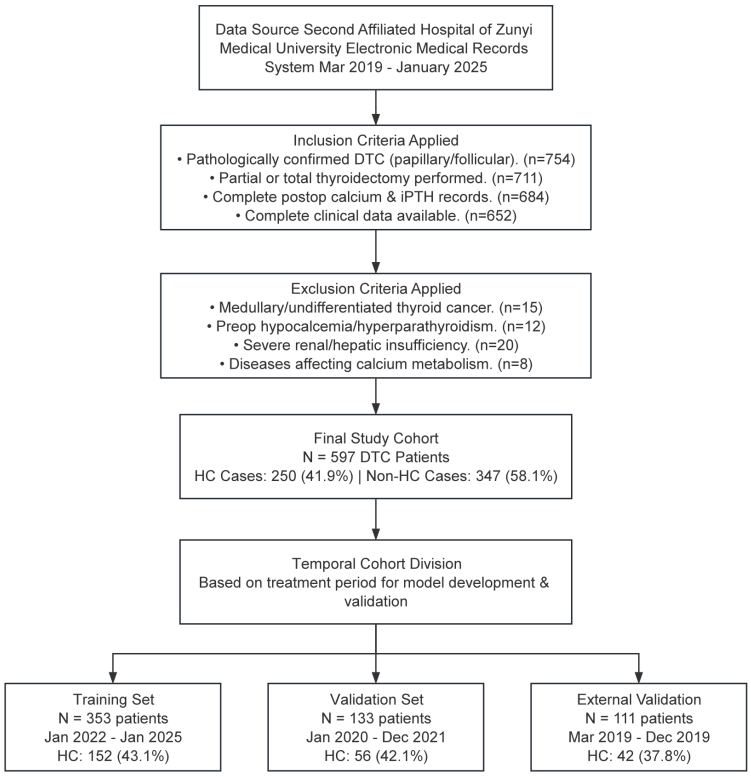

Figure 1. Sample screening flow chart.

Exclusion criteria: 1. Patients diagnosed with medullary/undifferentiated thyroid carcinomas or other undifferentiated thyroid cancers, to avoid interference from disease heterogeneity on HC analysis; 2. Patients with preoperative HC/hyperparathyroidism/hypoparathyroidism, ensuring that HC as a postoperative complication rather than a pre-existing condition; 3. Patients with severe renal/hepatic insufficiency or diseases influencing calcium metabolism (such as osteoporosis or vitamin D deficiency), to reduce confounding factors.

Clinical data collection

In this study, patient-related information was retrieved from the electronic medical record system and outpatient review records. Variable selection was based on a comprehensive literature review and clinical experience, focusing on factors previously identified as associated with postoperative HC or those with potential clinical relevance to parathyroid function. The selected variables included: General features: age (≥40 vs. <40 years), gender (male/female), BMI (<23, 23-24.9, or >25 kg/m^2), marital status (married/others), education level (≥ high school vs. < high school), hypertension (yes/no), diabetes (yes/no); Surgical factors: thyroidectomy extent (bilateral/unilateral), CCLND (yes/no), lateral compartment lymph node dissection (LCLND) (yes/no), surgical time (minutes, ≥82.5 vs. <82.5), intraoperative bleeding (IOB; mL, ≥25.5 vs. <25.5); Pathological characteristics: postoperative pathological subtype (papillary/follicular carcinoma), capsular invasion (yes/no), Tumor, Node, Metastasis [TNM] staging (I/II), tumor diameter (cm); Postoperative biochemical indicators: postoperative iPTH level (pmol/L), HC (corrected calcium <2.1 mmol/L or symptomatic, yes/no). Postoperative pathology was reviewed by at least two pathologists, and blood calcium and iPTH levels were assayed in standardized laboratories.

Statistical methods

All statistical analyses were completed using SPSS 26.0 and R 4.3.3. For categorical data, the number of cases (composition ratio) was used for statistical description, with differences assessed using chi-square tests (χ^2) or corrected χ^2 tests (between groups), and Kruskal-Wallis tests (among multiple groups). Continuous variables were first subjected to Kolmogorov-Smirnov (K-S) testing for normality. For normally distributed data, results were presented as mean ± standard deviation [X±S] and compared using t-tests. Non-normally distributed data were expressed as median [M] with interquartile range [IQR] and compared using the Mann-Whitney U tests (rank-sum test).

A systematic two-stage variable selection approach was employed for risk factor identification. Initially, all pre-selected variables, based on literature review and clinical relevance, were included in univariate logistic regression analysis to ensure comprehensive evaluation, regardless of their univariable significance. Variables demonstrating significant

associations in univariable analysis (P<0.05) were then included in the multivariate logistic regression model using the enter method. This approach ensures that only variables with demonstrated univariable significance contribute to the final model, reducing overfitting while maintaining clinical interpretability. While statistical significance (P<0.05) served as the primary inclusion criterion for multivariable analysis, variables with established clinical importance for parathyroid function were retained in sensitivity analyses, regardless of their *p*-values, to ensure clinical validity. Prior to multivariable modeling, variance inflation factor (VIF) analysis was performed to evaluate collinearity between variables, with VIF values <5 considered acceptable for inclusion. The final multivariable model identified independent predictors with their odds ratios (ORs), corresponding 95% confidence intervals, and statistical significance (*P* values) reported. In addition, parameters such as regression coefficients, standard errors, and Z-statistics were obtained through interaction effect analysis. Based on multivariable regression findings, R 4.3.3 was utilized for Nomogram prediction modeling, with model performance assessed using the following methods: discrimination ability was evaluated through Receiver operating characteristic (ROC) curve analysis and AUC calculation; calibration was assessed through calibration plots combined with mean absolute error (MAE), mean squared error (MSE), the 90th percentile of absolute errors, and goodness-of-fit (GOF) test *P*-value; robustness was evaluated using bootstrapping (1000 repetitions) to calculate Dxy, the coefficient of determination (R^2), calibration slope, and maximum absolute error; clinical utility was quantified through decision curve analysis (DCA) to determine net benefits across different probability thresholds.

The enter method was chosen over stepwise regression to maintain transparency in variable selection and to avoid the statistical instability associated with automated selection procedures. Complete case analysis was performed, and missing data patterns were evaluated to ensure no systematic bias in exclusions. Throughout all statistical analyses, a two-tailed *P*-value threshold of 0.05 was applied for determining statistical significance.

Results

Analysis of risk factors for postoperative HC in DTC

This study investigated the risk factors associated with postoperative HC in DTC patients, identifying several significant predictors. Elevated BMI (P=0.048), a history of diabetes (P<0.001), bilateral thyroidectomy (P<0.001), CCLND (P<0.001), LCLND (P<0.001), capsular invasion (P<0.001), prolonged surgery (P< 0.001), greater intraoperative bleeding (IOB) (P<0.001), and reduced postoperative iPTH levels (P<0.001) were all associated with a higher incidence of HC. Conversely, factors such as age, sex, marital status, education level, hypertension history, postoperative pathological subtype, and TNM staging showed no significant correlation with HC (P>0.05) (**Table 1**).

Comparison of clinical feature among training, validation, and external validation sets

Clinical features were compared across the training, validation, and external validation cohorts. No significant differences were found among the three cohorts in terms of age (P=0.477), sex (P=0.683), BMI (P=0.361), marital status (P=0.681), education level (P=0.758), hypertension history (P=0.429), diabetes history (P=0.235), thyroidectomy extent (P=0.367), CCLND (P=0.099), LCLND (P=0.146), postoperative pathological subtype (P=0.059), capsular invasion (P=0.925), TNM staging (P=0.144), tumor diameter (P=0 522), surgical time (P= 0.379), IOB (P=0.338), or postoperative iPTH levels (P=0.431). The homogeneous distribution of all evaluated variables confirmed the comparability among the three cohorts, which lays the foundation for both model development and subsequent validation (**Table 2**).

Comparison of clinical characteristics between groups with and without postoperative HC (training set)

Significant correlations were observed between postoperative HC and the following variables (all P<0.001): diabetes history, thyroidectomy extent, CCLND, LCLND, capsular invasion, tumor diameter, surgical time, IOB, and postoperative iPTH. Specifically, patients with a diabe-

Table 1. Comparative analysis of clinical features in differentiated thyroid cancer patients with and without postoperative HC

Variable	Total	HC group (n=250)	Non-HC group (n=347)	Statistic	P
Age				0.195	0.658
≥40 years old	343 (57.45%)	141 (56.40%)	202 (58.21%)		
<40	254 (42.55%)	109 (43.60%)	145 (41.79%)		
Sex				0.678	0.410
Male	107 (17.92%)	41 (16.40%)	66 (19.02%)		
Female	490 (82.08%)	209 (83.60%)	281 (80.98%)		
Body mass index				6.077	0.048
<23 kg/m^2	155 (25.96%)	60 (24.00%)	95 (27.38%)		
23-24.9 kg/m^2	400 (67.00%)	165 (66.00%)	235 (67.72%)		
>25 kg/m^2	42 (7.04%)	25 (10.00%)	17 (4.90%)		
Marital status				0.172	0.679
Married	487 (81.57%)	202 (80.80%)	285 (82.13%)		
Others	110 (18.43%)	48 (19.20%)	62 (17.87%)		
Educational level				1.291	0.256
≥ High school	318 (53.27%)	140 (56.00%)	178 (51.30%)		
< High school	279 (46.73%)	110 (44.00%)	169 (48.70%)		
Hypertension history				0.727	0.394
Yes	80 (13.40%)	30 (12.00%)	50 (14.41%)		
No	517 (86.60%)	220 (88.00%)	297 (85.59%)		
Diabetes history				42.646	<0.001
Yes	107 (17.92%)	75 (30.00%)	32 (9.22%)		
No	490 (82.08%)	175 (70.00%)	315 (90.78%)		
Thyroidectomy extent				33.398	<0.001
Bilateral	152 (25.46%)	94 (37.60%)	58 (16.71%)		
Unilateral	445 (74.54%)	156 (62.40%)	289 (83.29%)		
Central compartment lymph node dissection				41.487	<0.001
Yes	280 (46.90%)	156 (62.40%)	124 (35.73%)		
No	317 (53.10%)	94 (37.60%)	223 (64.27%)		
Lateral compartment lymph node dissection				30.987	<0.001
Yes	169 (28.31%)	101 (40.40%)	68 (19.60%)		
No	428 (71.69%)	149 (59.60%)	279 (80.40%)		
Postoperative pathological subtype				0.266	0.606
Papillary carcinoma	565 (94.64%)	238 (95.20%)	327 (94.24%)		
Follicular carcinoma	32 (5.36%)	12 (4.80%)	20 (5.76%)		
Capsular invasion				50.588	<0.001
Yes	154 (25.80%)	102 (40.80%)	52 (14.99%)		
No	443 (74.20%)	148 (59.20%)	295 (85.01%)		
TNM staging				1.509	0.219
I	237 (39.70%)	92 (36.80%)	145 (41.79%)		
II	360 (60.30%)	158 (63.20%)	202 (58.21%)		
Tumor diameter (cm)	3.14 [2.58, 3.66]	3.17 [2.66, 3.66]	3.08 [2.56, 3.64]	1.008	0.314
Surgical time (min)	80.88±10.77	87.32±10.50	76.25±8.30	-14.376	<0.001
Intraoperative bleeding (mL)	20.00 [12.00, 29.00]	28.00 [20.00, 34.00]	15.00 [9.00, 23.00]	11.626	<0.001
Postoperative iPTH (pmol/L)	1.54 [0.70, 3.10]	0.79 [0.44, 1.38]	2.65 [1.33, 3.98]	13.456	<0.001

Note: HC, hypocalcemia; TNM, Tumor, Node, Metastasis; iPTH, intact parathyroid hormone.

tes history, bilateral thyroidectomy, CCLND, LCLND, capsular invasion, larger tumor diameter, longer surgical time, greater IOB, and lower postoperative iPTH levels were more likely to develop HC. In contrast, no significant associations were found for age (P=0.730), sex (P=0.632), BMI (P=0.055), marital status (P=0.938), education level (P=0.473), hypertension history (P=0.194), pathological subtype (P=0.733), or TNM staging (P=0.092; **Table 3**).

Table 2. Comparison of clinical feature across training, validation, and external validation sets

Variable	Total	Training set (n=353)	Validation set (n=133)	External validation set (n=111)	Statistic	P
Age					1.481	0.477
≥40 years old	343 (57.45%)	210 (59.49%)	72 (54.14%)	61 (54.95%)		
<40	254 (42.55%)	143 (40.51%)	61 (45.86%)	50 (45.05%)		
Sex					0.762	0.683
Male	107 (17.92%)	62 (17.56%)	27 (20.30%)	18 (16.22%)		
Female	490 (82.08%)	291 (82.44%)	106 (79.70%)	93 (83.78%)		
Body mass index					4.346	0.361
<23 kg/m^2	155 (25.96%)	98 (27.76%)	35 (26.32%)	22 (19.82%)		
23-24.9 kg/m^2	400 (67.00%)	227 (64.31%)	91 (68.42%)	82 (73.87%)		
>25 kg/m^2	42 (7.04%)	28 (7.93%)	7 (5.26%)	7 (6.31%)		
Marital status					0.769	0.681
Married	487 (81.57%)	284 (80.45%)	110 (82.71%)	93 (83.78%)		
Others	110 (18.43%)	69 (19.55%)	23 (17.29%)	18 (16.22%)		
Educational level					0.554	0.758
≥ High school	318 (53.27%)	192 (54.39%)	70 (52.63%)	56 (50.45%)		
< High school	279 (46.73%)	161 (45.61%)	63 (47.37%)	55 (49.55%)		
Hypertension history					1.691	0.429
Yes	80 (13.40%)	42 (11.90%)	21 (15.79%)	17 (15.32%)		
No	517 (86.60%)	311 (88.10%)	112 (84.21%)	94 (84.68%)		
Diabetes history					2.900	0.235
Yes	107 (17.92%)	60 (17.00%)	21 (15.79%)	26 (23.42%)		
No	490 (82.08%)	293 (83.00%)	112 (84.21%)	85 (76.58%)		
Thyroidectomy extent					2.003	0.367
Bilateral	152 (25.46%)	90 (25.50%)	29 (21.80%)	33 (29.73%)		
Unilateral	445 (74.54%)	263 (74.50%)	104 (78.20%)	78 (70.27%)		
Central compartment lymph node dissection					4.619	0.099
Yes	280 (46.90%)	154 (43.63%)	65 (48.87%)	61 (54.95%)		
No	317 (53.10%)	199 (56.37%)	68 (51.13%)	50 (45.05%)		
Lateral compartment lymph node dissection					3.844	0.146
Yes	169 (28.31%)	99 (28.05%)	45 (33.83%)	25 (22.52%)		
No	428 (71.69%)	254 (71.95%)	88 (66.17%)	86 (77.48%)		
Postoperative pathological subtype					5.671	0.059
Papillary carcinoma	565 (94.64%)	340 (96.32%)	121 (90.98%)	104 (93.69%)		
Follicular carcinoma	32 (5.36%)	13 (3.68%)	12 (9.02%)	7 (6.31%)		
Capsular invasion					0.155	0.925
Yes	154 (25.80%)	91 (25.78%)	33 (24.81%)	30 (27.03%)		
No	443 (74.20%)	262 (74.22%)	100 (75.19%)	81 (72.97%)		
TNM staging					3.870	0.144
I	237 (39.70%)	148 (41.93%)	54 (40.60%)	35 (31.53%)		
II	360 (60.30%)	205 (58.07%)	79 (59.40%)	76 (68.47%)		
Tumor diameter (cm)	3.14 [2.58, 3.66]	3.13 [2.55, 3.59]	3.08 [2.57, 3.67]	3.21 [2.76, 3.73]	1.301	0.522
Surgical time (min)	80.00 [74.00, 88.00]	80.00 [73.00, 88.00]	79.00 [74.00, 86.00]	81.00 [75.00, 91.00]	1.943	0.379
Intraoperative bleeding (mL)	20.00 [12.00, 29.00]	21.00 [13.00, 29.00]	19.00 [11.00, 27.00]	20.00 [11.00, 30.00]	2.167	0.338
Postoperative iPTH (pmol/L)	1.54 [0.70, 3.10]	1.56 [0.69, 3.15]	1.66 [0.90, 3.07]	1.31 [0.65, 3.00]	1.683	0.431

Note: TNM, Tumor, Node, Metastasis; iPTH, intact parathyroid hormone.

Risk factors of postoperative HC in DTC: univariate and multivariate logistic regression analysis and variable collinearity test

To identify risk factors for postoperative HC in DTC patients, both univariate and multivariate logistic regression analyses were conducted, alongside VIF analysis to evaluate collinearity between variables. The VIF values of the variables included (diabetes history, thyroidectomy extent, CCLND, LCLND, capsular invasion, surgical time, and IOB) were all approximated 1,

Table 3. Comparison of clinical characteristics between HC and non-HC groups in the training set

Variable	Total	HC group (n=152)	Non-HC group (n=201)	Statistic	P
Age				0.119	0.730
≥40 years old	210 (59.49%)	92 (60.53%)	118 (58.71%)		
<40	143 (40.51%)	60 (39.47%)	83 (41.29%)		
Sex				0.230	0.632
Male	62 (17.56%)	25 (16.45%)	37 (18.41%)		
Female	291 (82.44%)	127 (83.55%)	164 (81.59%)		
Body mass index				5.807	0.055
<23 kg/m^2	98 (27.76%)	35 (23.03%)	63 (31.34%)		
23-24.9 kg/m^2	227 (64.31%)	100 (65.79%)	127 (63.18%)		
>25 kg/m^2	28 (7.93%)	17 (11.18%)	11 (5.47%)		
Marital status				0.006	0.938
Married	284 (80.45%)	122 (80.26%)	162 (80.60%)		
Others	69 (19.55%)	30 (19.74%)	39 (19.40%)		
Educational level				0.515	0.473
≥ High school	192 (54.39%)	86 (56.58%)	106 (52.74%)		
< High school	161 (45.61%)	66 (43.42%)	95 (47.26%)		
Hypertension history				1.689	0.194
Yes	42 (11.90%)	22 (14.47%)	20 (9.95%)		
No	311 (88.10%)	130 (85.53%)	181 (90.05%)		
Diabetes history				18.833	<0.001
Yes	60 (17.00%)	41 (26.97%)	19 (9.45%)		
No	293 (83.00%)	111 (73.03%)	182 (90.55%)		
Thyroidectomy extent				12.345	<0.001
Bilateral	90 (25.50%)	53 (34.87%)	37 (18.41%)		
Unilateral	263 (74.50%)	99 (65.13%)	164 (81.59%)		
Central compartment lymph node dissection				20.108	<0.001
Yes	154 (43.63%)	87 (57.24%)	67 (33.33%)		
No	199 (56.37%)	65 (42.76%)	134 (66.67%)		
Lateral compartment lymph node dissection				13.528	<0.001
Yes	99 (28.05%)	58 (38.16%)	41 (20.40%)		
No	254 (71.95%)	94 (61.84%)	160 (79.60%)		
Postoperative pathological subtype				0.116	0.733
Papillary carcinoma	340 (96.32%)	147 (96.71%)	193 (96.02%)		
Follicular carcinoma	13 (3.68%)	5 (3.29%)	8 (3.98%)		
Capsular invasion				26.166	<0.001
Yes	91 (25.78%)	60 (39.47%)	31 (15.42%)		
No	262 (74.22%)	92 (60.53%)	170 (84.58%)		
TNM staging				2.834	0.092
I	148 (41.93%)	56 (36.84%)	92 (45.77%)		
II	205 (58.07%)	96 (63.16%)	109 (54.23%)		
Tumor diameter (cm)	80.90±11.03	87.89±10.50	75.62±8.12	-12.380	<0.001
Surgical time (min)	21.00 [13.00, 29.00]	27.50 [18.00, 34.00]	16.00 [11.00, 24.00]	7.701	<0.001
Intraoperative bleeding (mL)	20.00 [12.00, 29.00]	28.00 [20.00, 34.00]	15.00 [9.00, 23.00]	11.619	<0.001
Postoperative iPTH (pmol/L)	1.56 [0.69, 3.15]	0.78 [0.42, 1.38]	2.65 [1.34, 3.96]	-10.306	<0.001

Note: HC, hypocalcemia; TNM, Tumor, Node, Metastasis; iPTH, intact parathyroid hormone.

suggesting no significant multicollinearity among these variables, confirming their suitability for regression modeling (**Table 4**).

Univariate analysis revealed significant associations (P<0.001) for the following variables: diabetes history (OR=3.538), thyroidectomy extent (OR=2.373), CCLND (OR=2.677), LCLND (OR=2.408), capsular invasion (OR=3.576), surgical time (OR=9.292), and IOB (OR=6.227). Subsequently, multivariate analysis identified diabetes history (OR=3.132, P=0.006), thyroidectomy extent (OR=2.142, P=0.023), LCLND (OR=2.011, P=0.037), capsular invasion (OR=

Table 4. Assignment and collinearity test (VIF values) of hypocalcemia-related variables

Variable	Variable type	Assignment content	VIF
Diabetes history	(X)	Yes =1, no =0	1.0133
Thyroidectomy extent	(X)	Bilateral =1, unilateral =0	1.0135
Central compartment lymph node dissection	(X)	Yes =1, no =0	1.0127
Lateral compartment lymph node dissection	(X)	Yes =1, no =0	1.0182
Capsular invasion	(X)	Yes =1, no =0	1.0256
Surgical time	(X)	≥82.5 =1, <82.5 =0	1.0365
Intraoperative bleeding (mL)	(X)	≥25.5 =1, <25.5 =0	1.0232
Hypocalcemia	(Y)	Yes =1, no =0	1.0133

Note: VIF, Variance Inflation Factor.

Table 5. Univariate and multivariate logistic regression analysis of hypocalcemia after differentiated thyroid cancer surgery

Variable name	Univariate			Multivariate		
	OR	P	95% CI	OR	P	95% CI
Diabetes history	3.538	<0.001	1.956-6.402	3.132	0.006	1.4-7.235
Thyroidectomy extent	2.373	<0.001	1.456-3.867	2.142	0.023	1.117-4.156
Central compartment lymph node dissection	2.677	<0.001	1.733-4.136	1.676	0.088	0.924-3.041
Lateral compartment lymph node dissection	2.408	<0.001	1.499-3.869	2.011	0.037	1.046-3.914
Capsular invasion	3.576	<0.001	2.164-5.91	3.196	<0.001	1.648-6.343
Surgical time	9.292	<0.001	5.702-15.143	10.843	<0.001	6.014-20.348
Intraoperative bleeding	6.227	<0.001	3.857-10.051	7.493	<0.001	4.12-14.13

Note: OR, odds ratio; CI, confidence interval.

3.196, P<0.001), surgical time (OR=10.843, P<0.001), and IOB (OR=7.493, P<0.001) as independent risk factors for postoperative HC. However, CCLND (OR=1.676, P=0.088) did not show statistical significance (**Table 5**).

Interaction analysis of HC with risk factors

The interaction between postoperative HC and risk factors was evaluated through regression analysis. Variables significantly associated with HC included diabetes history (P=0.003), thyroidectomy extent (P=0.033), LCLND (P=0.023), capsular invasion (P=0.001), surgical time (P<0.001), and IOB (P<0.001). The regression coefficients for these factors indicated their statistically significant predictive value for HC risk. Specifically, IOB (Estimate =0.083) and surgical time (Estimate =0.159) emerged as the strongest predictors, followed by capsular invasion (Estimate =1.124), diabetes history (Estimate =1.254), thyroidectomy extent (Estimate =0.738), and LCLND (Estimate =0.785). These variables amplified HC risk through interaction effects, suggesting that bilateral thyroidectomy, LCLND, and tumor invasion characteristics may increase the risk due to parathyroid injury or tissue destruction. The model's intercept term (P<0.001) confirmed its robust fit. Therefore, it is suggested to comprehensively consider these predictors in clinical practice to optimize preoperative evaluation and intraoperative strategies, thus mitigating HC risk (**Table 6** and **Figure 2**).

Nomogram development for predicting postoperative HC risk in DTC and analysis of key risk factors

A Nomogram predictive model was developed to evaluate the likelihood of postoperative HC in DTC patients, utilizing the regression analysis results. The model incorporated the significant risk factors identified, including diabetes history, thyroidectomy extent, LCLND, capsular invasion, surgical time, and IOB. The results established surgical time and IOB as the most significant predictors of HC risk. Additionally, diabetes history, thyroidectomy extent, LCLND, and capsular invasion also contributed substantially to HC risk. The model quantified the weight of each factor through the integral sys-

Table 6. Interaction analysis of hypocalcemia and risk factors

Variable	Estimate	Std. Error	z value	Pr (>|z|)
(Intercept)	-15.945	1.793	-8.895	<0.001
Diabetes history	1.254	0.427	2.937	0.003
Thyroidectomy extent	0.738	0.346	2.131	0.033
Lateral compartment lymph node dissection	0.785	0.346	2.269	0.023
Capsular invasion	1.124	0.343	3.279	0.001
Surgical Time (min)	0.159	0.020	7.899	<0.001
Intraoperative bleeding (ml)	0.083	0.016	5.241	<0.001

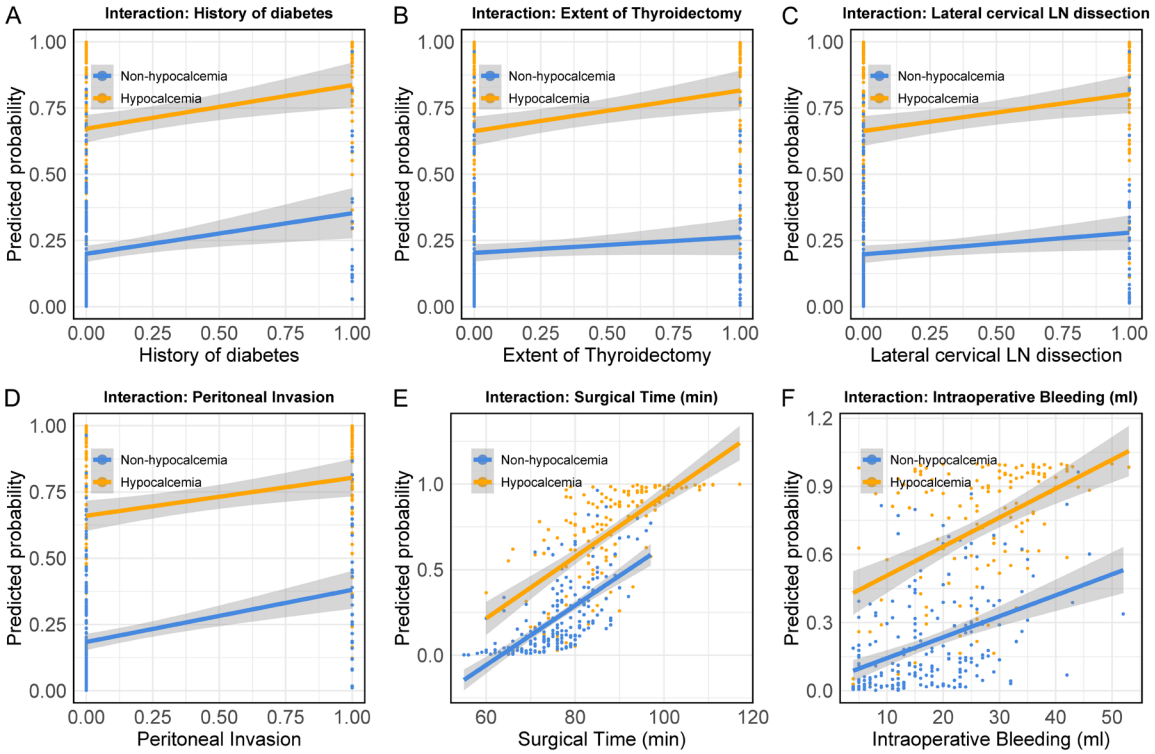

Figure 2. Interaction plot of hypocalcemia with risk factors. Interaction analysis between HC and diabetes history (A), thyroidectomy extent (B), lateral compartment lymph node dissection (C), capsular invasion (D), surgical time (E), and intraoperative bleeding (F).

tem, in which surgical time (≥82.5 minutes) and IOB (≥25.5 ml) carried the highest weight in the total score (**Figure 3**).

Validation analysis of the postoperative HC risk prediction model in DTC in the training set

The performance of the HC risk prediction model after DTC surgery was validated in the training set. ROC analysis demonstrated strong model discrimination (AUC=0.888). The calibration curve demonstrated a close alignment between predicted probabilities and observed outcomes, with MAE, MSE, absolute error at the 90th percentile, and GOF test *P*-value being 0.022, 0.00062, 0.037, and 0.0469, respectively, indicating robust calibration. The Bootstrap validation (1000 repetitions) yielded a Dxy of 0.7773, an R^2 of 0.5578, a slope of 1.0025, and a maximum absolute error of 0.0007, supporting the model's favorable prediction stability and generalizability. DCA curve analysis showed the model's net clinical benefit across the 0-99% threshold range, peaking at 56.94%, suggesting the model's high clinical application value (**Figure 4**).

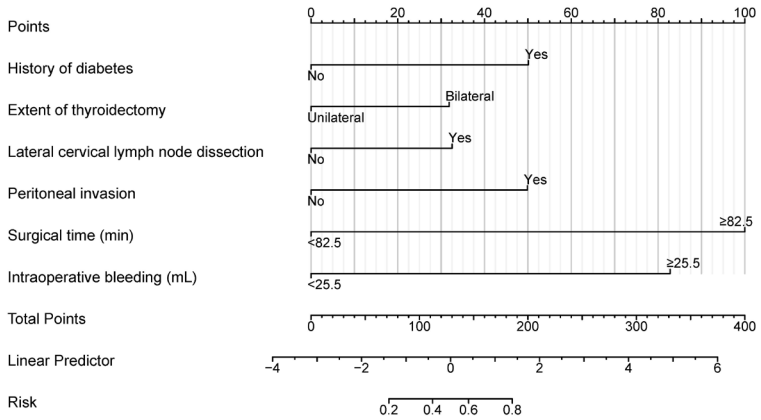

Figure 3. Nomogram for postoperative hypocalcemia risk prediction in differentiated thyroid cancer.

Performance analysis of the postoperative HC risk prediction model in DTC in the validation set

The performance of the HC risk prediction model after DTC surgery was further evaluated in the validation set. ROC analysis yielded an AUC of 0.866, indicating excellent discrimination capability. The calibration curve showed that the model's predicted values closely aligned with the actual observed values, manifested as an MAE of 0.025, an MSE of 0.00126, a 0.9 quantile absolute error of 0.054, and a *P*-value of 0.0973 for the GOF test, indicating a good calibration. Bootstrap resampling (1,000 iterations) validated the model's robustness and generalizability, as evidenced by a Dxy statistic of 0.7311, an R^2 of 0.4812, a slope of 0.9969, and a maximum absolute error of 0.0024. DCA further demonstrated the model's clinical utility, with net benefits observed across the 0-93% probability threshold range and a peak net benefit rate of 62.40%, underscoring its high clinical application potential (**Figure 5**).

Performance evaluation of the postoperative HC risk prediction in DTC in the external validation cohort

This study further evaluated the postoperative HC risk predictive model in DTC patients using an independent validation cohort (n=111 cases). The model exhibited outstanding discrimination capability, as evidenced by an AUC of 0.913. In the aspect of calibration performance evaluation, the predicted probability showed good consistency with the actual observation results, with an MAE of 0.019, an MSE of 0.00053, and a 90th percentile absolute error of 0.038; the GOF test *P*-value of 0.8586 further proved the mode's ideal calibration effects. The indexes obtained by Bootstrap validation with 1000 iterations included a Dxy of 0.8246, an R^2 of 0.6434, a slope of 0.9708, and a maximum absolute error of 0.0078, confirming the model's stability and excellent generalization capacity. Clinical utility assessment through DCA curve analysis indicated significant net benefits across 0-97% threshold probability, achieving maximum clinical utility of 63.90%, which strongly supports the important application value of the prediction model in clinical practice (**Figure 6**).

Comparative evaluation of the risk prediction model versus postoperative iPTH for HC after DTC surgery

This study compared the predictive performance of the postoperative HC risk prediction model with postoperative iPTH-based predictions across the training, validation, and external validation sets. In the training cohort, the Risk model demonstrated superior predictive capability compared to postoperative iPTH (Z=2.353, P=0.019), with an AUC improvement of 0.068 (95% CI: 0.011-0.124). In the validation set, no significant difference was found between the Risk model and postoperative iPTH-based prediction (Z=0.851, P=0.395), with an AUC difference of 0.040 (95% CI: -0.052-0.132). However, in the external validation cohort, the Risk model significantly outperformed postoperative iPTH (Z=2.037, P=0.042), showing an AUC improvement of 0.098 (95% CI: 0.004-0.192). These results indicate that the risk prediction model performs better in predicting HC than single postoperative iPTH level across both training and external validation datasets, particularly demonstrating strong generalizability in the external validation cohort, providing a more reliable prediction tool for clinical applications (**Figure 7** and **Table 7**).

Discussion

Differentiated thyroid cancer (DTC), the predominant histological subtype (>90%) of thy-

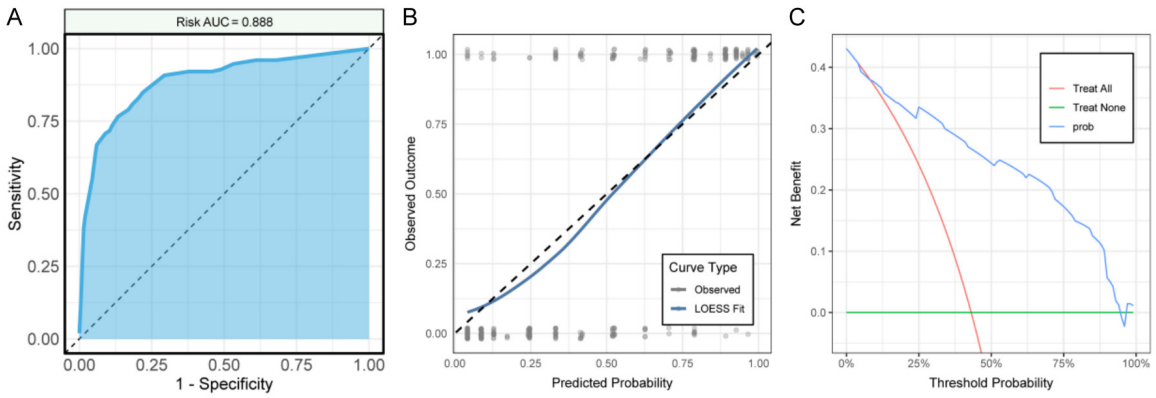

Figure 4. Performance assessment of the risk prediction model for postoperative hypocalcemia in the training set. A. ROC. B. Calibration curve. C. DCA. Note: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

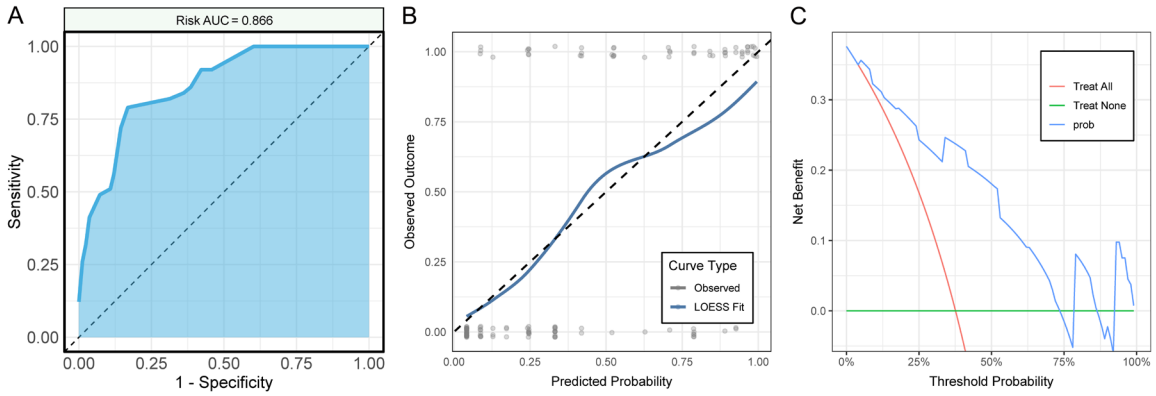

Figure 5. Performance assessment of the risk prediction model for postoperative hypocalcemia in the validation set. A. ROC. B. Calibration curve. C. DCA. Note: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

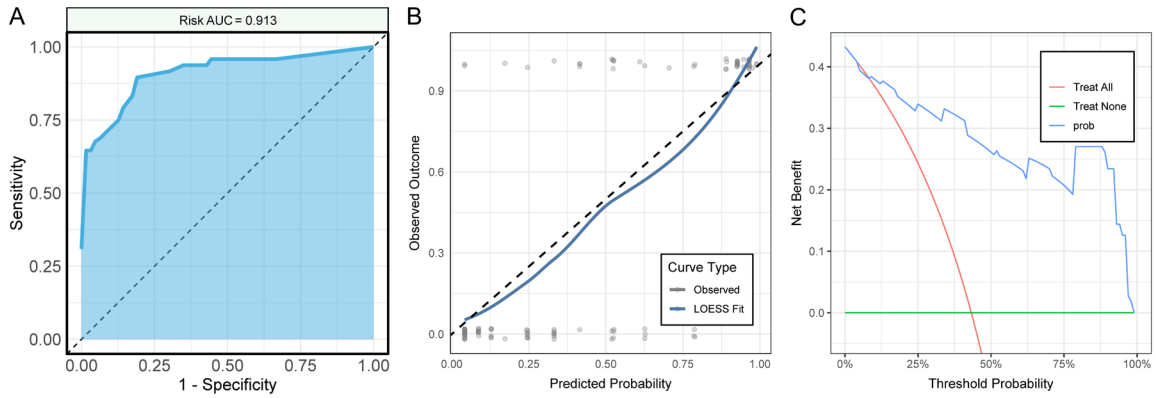

Figure 6. Performance assessment of the risk prediction model for postoperative hypocalcemia in the external validation set. A. ROC. B. Calibration curve. C. DCA. Note: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

roid malignancies, has shown rising incidence due to widespread health screening [19]. Despite excellent prognosis, with 5-year survival rates exceeding 95%, about 20%-50% of

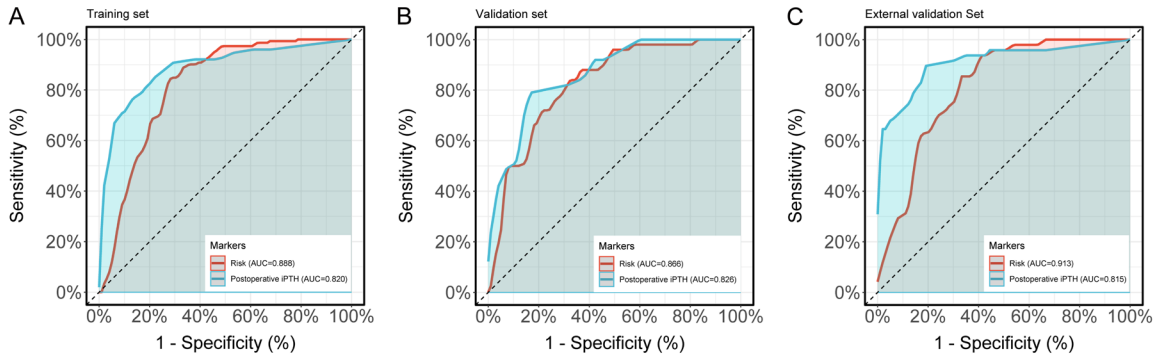

Figure 7. Comparative evaluation of the Risk model versus postoperative iPTH for post-operative hypocalcemia in three cohorts. A. Training cohort: Risk vs. postoperative iPTH. B. Validation cohort: Risk vs. postoperative iPTH. C. External validation cohort: Risk vs. postoperative iPTH. Note: iPTH, intact parathyroid hormone.

Table 7. Comparative evaluation of the Risk model versus postoperative iPTH for postoperative hypocalcemia

Marker 1	Marker 2	Z_value	*P*_value	AUC_difference	CI_lower_upper
Training set risk	Postoperative iPTH	2.353	0.019	0.068	0.011-0.124
Validation set risk	Postoperative iPTH	0.851	0.395	0.04	-0.052-0.132
External validation set risk	Postoperative iPTH	2.037	0.042	0.098	0.004-0.192

Note: AUC, area under the curve; CI, confidence interval; iPTH, intact parathyroid hormone.

DTC patients develop HC following surgery, which leads to complications such as hand-foot convulsions, arrhythmia, prolonged hospitalization, and increased healthcare costs [20]. Existing research primarily focuses on individual markers, with most prediction models lacking external validation, resulting in limited predictive efficacy, especially in the case of postoperative intact parathyroid hormone (iPTH) [15, 21]. By analyzing 597 DTC cases, this study comprehensively evaluated HC risk determinants and constructed a validated Nomogram model, providing accurate tools for preoperative risk stratification and postoperative management, ultimately optimizing clinical prevention strategies.

Through logistic regression analysis, this study identified diabetes history, bilateral thyroidectomy, LCLND, capsular invasion, surgical time, and IOB as independent risk factors for postoperative HC in DTC patients. Choe et al. [22] similarly found that tumor multifocality and low preoperative calcium levels significantly increased HC risk in pediatric thyroid cancer patients, supporting the correlation between tumor invasiveness and HC. Other studies also suggest that thyroid nodules >4 cm and low preoperative calcium levels predict HC [23], further emphasizing the importance of preoperative tumor invasiveness evaluation.

Diabetes may impact parathyroid function through microangiopathy or metabolic disorders. Chronic hyperglycemia may impair parathyroid blood supply or cellular function, reducing parathyroid hormone secretion and increasing the risk of HC. Additionally, metabolic diseases like Graves' disease similarly increase postoperative HC susceptibility [24]. These findings underscore the need for preoperative glycemic control and thorough parathyroid function evaluation to reduce HC risk.

Bilateral thyroidectomy involves bilateral parathyroid glands due to expanded operative scope, increasing the risk of direct injury or disruption of blood supply. This risk is particularly heightened in patients with complex anatomical variations or significant scar tissue formation, necessitating fine operative techniques and microscopic visualization for parathyroid protection [25]. Shuchleib-Cung et al. [26] found that intraoperative parathyroid damage substantially elevated HC risk, especially following bilateral thyroidectomy, emphasizing the necessity of delicate surgical maneuvers.

LCLND may damage vascular and lymphatic circulation that supplies the parathyroid glands through extensive dissection, resulting in potential functional impairment. In contrast, CCLND has a relatively limited scope, impacting the parathyroid glands to a lesser extent [27], possibly explaining its non-significant association with HC in multivariate assessments. However, Lim et al. [28] suggested an increased delayed HC risk following CCLND, which contrasts with our results and highlights the variable effects of dissection range on parathyroid function.

Capsular invasion increases the surgical complexity due to enhanced tumor aggressiveness. Tumors with capsular invasion may directly compress or erode parathyroid glands and their vasculature, raising the likelihood of injury during resection. Our study provides new evidence linking tumor invasion to postoperative HC, underscoring the significance of preoperative imaging evaluation of tumor invasiveness in risk prediction [29].

Surgical time and IOB were identified as the strongest predictors, reflecting both surgical complexity and tissue injury severity. Prolonged operations can impair parathyroid microvasculature through continuous traction or electrocoagulation thermal damage, while IOB may disrupt parathyroid blood supply or cause hematoma compression, further compromising glandular function [30]. Wang et al. [31] also linked extended surgical time to intraoperative parathyroid injury, emphasizing the importance of optimizing surgical procedures, minimizing unnecessary dissection, and employing effective hemostasis techniques to reduce HC risk.

This study further analyzed the interaction effects among diabetes history, bilateral thyroidectomy, LCLND, capsular invasion, surgical time, and IOB. The analysis revealed that these factors significantly increased HC risk after DTC surgery. IOB and surgical time demonstrated the strongest predictive ability, particularly in interactions with capsular invasion and bilateral thyroidectomy. These interactions may stem from multiple factors, collectively affecting parathyroid function or blood supply mechanisms. Literature supports that near-infrared autofluorescence (NIRAF) technology significantly reduces HC rates [6], suggesting that intraoperative injury represents a core mechanism of interaction. The interaction between capsular invasion and bilateral thyroidectomy may heighten anatomical difficulty due to tumor aggressiveness, with tumor-induced compression or erosion further aggravating injury risk.

The constructed Nomogram model showed excellent discrimination across the training (AUC=0.888), validation (AUC=0.866), and external validation sets (AUC=0.913), demonstrating high accuracy in predicting postoperative HC risk. Calibration curve analysis and GOF test confirmed a high level of consistency between predicted probabilities and observed outcomes. Bootstrap analysis validated the model's robustness, with external validation data supporting its stability and broad generalizability. DCA confirmed significant net benefits across different risk thresholds, confirming the model's clinical utility.

Compared to postoperative iPTH-based predictions, our Nomogram model exhibited superior performance across both the training and external validation cohorts. Unlike iPTH, which is influenced by detection timing and laboratory standardization, our Nomogram integrates multidimensional predictors, including patient characteristics, surgical factors, pathological features, enabling more comprehensive and accurate predictions. Benmiloud et al. [32] found that NIRAF-assisted parathyroid identification significantly reduced HC rates, suggesting that intraoperative techniques can compensate for iPTH monitoring limitations. Furthermore, a meta-analysis by Weng et al. [33] revealed that NIRAF reduces both temporary and possibly permanent HC risk, further supporting the superior performance of our comprehensive model over single-indicator approaches.

Literature shows that although PTH, calcium, and phosphorus levels at one month postoperatively effectively predict permanent HC with high AUCs, the testing timepoint is late [34], underscoring the challenges of using iPTH for early prediction of HC. Zheng et al. [35] found that postoperative iPTH was significantly predictive of symptomatic HC in elderly patients, but this finding was population-specific, further strengthening the cross-population applicability advantages of our Nomogram. Additionally, Gao et al. [36] showed that despite high specificity of PTH level (<8.75 ng/L) on postoperative day 1 for predicting permanent hypoparathy-

roidism, its sensitivity was insufficient, further validating the deficiencies of relying on single iPTH measurements and highlighting the clinical utility of the Nomogram.

The proposed Nomogram model, by quantifying risk factors including diabetes history, bilateral thyroidectomy, LCLND, capsular invasion, surgical time, and IOB, provides a high-precision tool for accurate postoperative HC prevention and control in DTC patients. This model facilitates preoperative high-risk patient identification, enhances intraoperative parathyroid protection and IOB reduction, and enables postoperative individualized calcium supplementation. As a result, it contributes to reduced HC rates, shortened hospitalization, and improved patient quality of life.

However, certain limitations should be considered. Despite a sufficient sample size (597 cases), the limited validation set and the single-center design may restrict the model's applicability across different populations, including varying races or regions. Additionally, potential missing data or bias may exist in electronic health records, and factors such as parathyroid identification, autologous transplantation, or operator experience were not considered. Future multicenter, larger-scale prospective research, incorporating additional risk factors and integrating digital clinical decision support systems, should further explore the model's potential for long-term HC prediction, enhancing generalizability and clinical application value.

Conclusion

Diabetes history, bilateral thyroidectomy, lateral lymph node dissection, capsular invasion, prolonged surgical time (≥82.5 min), and increased intraoperative bleeding (≥25.5 mL) are key factors that elevate postoperative hypocalcemia risk in DTC patients. The Nomogram model, integrating these factors, outperforms iPTH predictions, offering a precise tool for preoperative risk assessment and postoperative management to reduce HC incidence and improve patient outcomes.

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Disclosure of conflict of interest

None.

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References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Han PZ, Ye WD, Yu PC, Tan LC, Shi X, Chen XF, He C, Hu JQ, Wei WJ, Lu ZW, Qu N, Wang Y, Ji QH, Ji DM and Wang YL. A distinct tumor microenvironment makes anaplastic thyroid cancer more lethal but immunotherapy sensitive than papillary thyroid cancer. JCI Insight 2024; 9: e173712.

[3] Sun XM, Pang F, Zhuang SM, Xie LE, Zhong QY and Liu TR. Tumor size rather than the thyroid invasion affects the prognosis of parathyroid carcinoma without lymph node or distant metastasis. Eur Arch Otorhinolaryngol 2022; 279: 4587-4594.

[4] Wang W, Ding Y, Jiang W and Li X. Can cervical lymph node metastasis increase the risk of distant metastasis in papillary thyroid carcinoma? Front Endocrinol (Lausanne) 2022; 13: 917794.

[5] Sun L, Lin X, Li N, Zhang Q, Jiang Y, Wang O, Xia W, Xing X, Li X and Li M. Effects of vitamin D(3) and calcium supplementation on bone of young adults after thyroidectomy of differentiated thyroid carcinoma. Endocrine 2025; 88: 836-846.

[6] Guerlain J, Breuskin I, Abbaci M, Lamartina L, Hadoux J, Baudin E, Al Ghuzlan A, Moog S, Marhic A, Villard A, Obongo R and Hartl DM. Intraoperative parathyroid gland identification using autofluorescence imaging in thyroid cancer surgery with central neck dissection: impact on post-operative hypocalcemia. Cancers (Basel) 2023; 16: 182.

[7] Bumber B, Potroško V, Vugrinec O, Ferenčaković M and Gršić K. Hypocalcemia after completion thyroidectomy for papillary thyroid carcinoma. Acta Clin Croat 2020; 59 Suppl 1: 136-145.

[8] Lee JW, Kim JK, Kwon H, Lim W, Moon BI and Paik NS. Routine low-dose calcium supplementation after thyroidectomy does not re-

duce the rate of symptomatic hypocalcemia: a prospective randomized trial. Ann Surg Treat Res 2019; 96: 177-184.
[9] Rubin SJ, Park JH, Pearce EN, Holick MF, McAneny D and Noordzij JP. Vitamin D status as a predictor of postoperative hypocalcemia after thyroidectomy. Otolaryngol Head Neck Surg 2020; 163: 501-507.
[10] Soelling SJ, Mahvi DA, Liu JB, Sheu NO, Doherty G, Nehs MA and Cho NL. Impact of obesity on risk of hypocalcemia after total thyroidectomy: targeted national surgical quality improvement program analysis of 16,277 patients. J Surg Res 2023; 291: 250-259.
[11] Casey C and Hopkins D. The role of preoperative vitamin D and calcium in preventing post-thyroidectomy hypocalcaemia: a systematic review. Eur Arch Otorhinolaryngol 2023; 280: 1555-1563.
[12] Mo K, Shang J, Wang K, Gu J, Wang P, Nie X and Wang W. Parathyroid hormone reduction predicts transient hypocalcemia after total thyroidectomy: a single-center prospective study. Int J Endocrinol 2020; 2020: 7189857.
[13] Păduraru DN, Ion D, Carsote M, Andronic O and Bolocan A. Post-thyroidectomy hypocalcemia - risk factors and management. Chirurgia (Bucur) 2019; 114: 564-570.
[14] Mattoo S, Agarwal A, Mayilvaganan S, Mishra P, Agarwal G, Mishra A, Chand G, Gupta SK and Mishra SK. Role of postoperative intact serum PTH as an early predictor of severe post-thyroidectomy hypocalcemia: a prospective study. J Endocrinol Invest 2021; 44: 1961-1970.
[15] Lee YH, Liu Z, Zheng L, Qiu J, Sang J and Guan W. The rate of postoperative decline in parathyroid hormone levels can predict symptomatic hypocalcemia following thyroid cancer surgery with neck lymph node dissection. Nutr Cancer 2025; 77: 1-8.
[16] Inversini D, Rausei S, Ferrari CC, Frattini F, Anuwong A, Kim HY, Liu X, Wu CW, Tian W, Liu R and Dionigi G. Early intact PTH (iPTH) is an early predictor of postoperative hypocalcemia for a safer and earlier hospital discharge: an analysis on 260 total thyroidectomies. Gland Surg 2016; 5: 522-528.
[17] Lacroix C, Potard G, Thuillier P, Le Pennec R, Prévot J, Roudaut N, Marianowski R and Leclere JC. Use of the parathyroid hormone assay at H6 post thyroidectomy: an early predictor of hypocalcemia. J Endocrinol Invest 2022; 45: 1-8.
[18] Zhuo Y, Fang H, Yuan J, Gong L and Zhang Y. Fine-needle aspiration biopsy evaluation-oriented thyroid carcinoma auxiliary diagnosis. Ultrasound Med Biol 2023; 49: 1173-1181.
[19] Li M, Hu M, Jiang L, Pei J and Zhu C. Trends in cancer incidence and potential associated factors in China. JAMA Netw Open 2024; 7: e2440381.
[20] Han B, Zheng R, Zeng H, Wang S, Sun K, Chen R, Li L, Wei W and He J. Cancer incidence and mortality in China, 2022. J Natl Cancer Cent 2024; 4: 47-53.
[21] Zhong LK, Gan XX, Deng XY, Shen F, Feng JH, Cai WS, Liu QY, Miao JH, Zheng BX and Xu B. Potential five-mRNA signature model for the prediction of prognosis in patients with papillary thyroid carcinoma. Oncol Lett 2020; 20: 2302-2310.
[22] Choe Y, Lee YJ, Shin CH, Chung EJ and Lee YA. Risk factors of postoperative hypoparathyroidism after total thyroidectomy in pediatric patients with thyroid cancer. Ann Pediatr Endocrinol Metab 2023; 28: 26-33.
[23] Halwani C, Turki S and Akkari K. Predictive factors for post-total thyroidectomy hypocalcaemia. Tunis Med 2020; 98: 720-725.
[24] Kazaure HS, Zambeli-Ljepovic A, Oyekunle T, Roman SA, Sosa JA, Stang MT and Scheri RP. Severe hypocalcemia after thyroidectomy: an analysis of 7366 patients. Ann Surg 2021; 274: e1014-e1021.
[25] Davis TME. Severe Hypomagnesemia and hypocalcemia linked to semaglutide in type 2 diabetes: a case report. Am J Case Rep 2025; 26: e946539.
[26] Shuchleib-Cung A, Garcia-Gordillo JA, Ferreira-Hermosillo A and Mercado M. Risk factors for hypocalcemia after total thyroidectomy. Cir Cir 2022; 90: 765-769.
[27] van Rooijen JJ, van Trotsenburg ASP, van de Berg DJ, Zwaveling-Soonawala N, Nieveen van Dijkum EJM, Engelsman AF, Derikx JPM and Mooij CF. Complications after thyroidectomy in children: lymph node dissection is a risk factor for permanent hypocalcemia. Front Endocrinol (Lausanne) 2021; 12: 717769.
[28] Lim ST, Jeon YW, Gwak H and Suh YJ. Incidence, risk factors, and clinical implications of delayed hypoparathyroidism on postoperative day two following total thyroidectomy for papillary thyroid carcinoma. Endocr Pract 2020; 26: 768-776.
[29] Chen Z, Zhao Q, Du J, Wang Y, Han R, Xu C, Chen X and Shu M. Risk factors for postoperative hypocalcaemia after thyroidectomy: a systematic review and meta-analysis. J Int Med Res 2021; 49: 0300060521996911.
[30] Coimbra C, Monteiro F, Oliveira P, Ribeiro L, de Almeida MG and Condé A. Hypoparathyroidism following thyroidectomy: predictive factors. Acta Otorrinolaringol Esp 2017; 68: 106-111.
[31] Wang TX, Yu WB, Ma X, Song YT and Zhang NS. Risk factors of hypoparathyroidism following total or near total thyroidectomy. Zhonghua Wai Ke Za Zhi 2016; 54: 206-211.

[32] Benmiloud F, Godiris-Petit G, Gras R, Gillot JC, Turrin N, Penaranda G, Noullet S, Chéreau N, Gaudart J, Chiche L and Rebaudet S. Association of autofluorescence-based detection of the parathyroid glands during total thyroidectomy with postoperative hypocalcemia risk: results of the PARAFLUO multicenter randomized clinical trial. JAMA Surg 2020; 155: 106-112.
[33] Weng YJ, Jiang J, Min L, Ai Q, Chen DB, Chen WC and Huang ZH. Intraoperative near-infrared autofluorescence imaging for hypocalcemia risk reduction after total thyroidectomy: evidence from a meta-analysis. Head Neck 2021; 43: 2523-2533.
[34] Cao B, Zhang C, Jiang M, Yang Y and Liu X. Development and validation of risk prediction models for permanent hypocalcemia after total thyroidectomy in patients with papillary thyroid carcinoma. Sci Rep 2025; 15: 9348.
[35] Zheng LL, Chen KH, Liu ZJ, Dai LH, Qin JB, Li YX and Guan WX. The predictive value of postoperative intact parathyroid hormone for symptomatic hypocalcemia in older patients with thyroid cancer. Gland Surg 2025; 14: 510-519.
[36] Gao J, Zhang Q, Wang Z, Guo Y, Liang S, Zhang Y and Qu K. Predictive value of PTH level on day 1 after surgery for papillary thyroid carcinoma in patients with permanent hypoparathyroidism. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2023; 37: 365-369.