Risk factors for thyroid hormone replacement therapy after hemithyroidectomy and development of a predictive nomogram

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Abstract

Purpose

Hemithyroidectomy is a valid operation to retain functional contralateral thyroid lobe that is indicated for a variety of thyroid diseases. This study aimed at determination of the risk factors for thyroid hormone replacement following hemithyroidectomy and to develop a predictive nomogram.

Methods

Data of patients treated by hemithyroidectomy for benign thyroid disease between January 2015 and January 2020 were retrospectively analyzed. Baseline characteristics, surgery-related variables, and preoperative and postoperative thyroid function of patients were collected from the case records and compared between patients with postoperative euthyroidism and patients with postoperative hypothyroidism. Postoperative euthyroidism patients without thyroid hormone replacement were compared to those who developed postoperative hypothyroidism with thyroid hormone replacement. The factors associated with thyroid hormone replacement were used to construct a binomial logistic-regression model and visualized as a predictive nomogram to evaluate the risk of thyroid hormone replacement following hemithyroidectomy.

Results

Of the 378 patients (74% female) included in the study, 110 (29.1%) developed postoperative hypothyroidism. Preoperative serum thyroid-stimulating hormone (TSH) > 2.172 μIU/mL was identified as an independent risk factor for postoperative hypothyroidism (odds ratio [OR] = 8.02; 95% confidence interval [CI]: 4.87-13.20; $P < 0.001$). Of 110 patients with postoperative hypothyroidism, 56 (50.9%) received thyroid hormone replacement. Unilateral thyroid nodule and preoperative serum TSH > 2.172 μIU/mL were independent predictors of postoperative thyroid hormone replacement ($P = 0.01$, and $P < 0.001$, respectively). Temporary subclinical hypothyroidism occurred in 12 patients; all 12 reverted to euthyroid state without thyroid hormone replacement. The discriminative effect of the binomial regression model was proved reliable by the Hosmer–Lemeshow goodness-of-fit test ($P = 0.856$), and predictive ability of the nomogram was satisfactory with a C-index of 0.85.

Conclusion

Hypothyroidism is common after hemithyroidectomy, and almost half of the patients will need thyroid hormone replacement. Elevated preoperative serum TSH level and unilateral thyroid nodule were independent predictors of thyroid hormone replacement following hemithyroidectomy. The predictive nomogram could be a useful tool for clinical practice.

Introduction

Hemithyroidectomy is performed for a variety of indications, including benign and malignant thyroid disease and pathologically indeterminate nodule (1, 2). Endogenous thyroid hormone (TH) secretion from the remained functional contralateral thyroid lobe usually fulfills the physiological need for TH (3). However, 11%-45% of patients will develop hypothyroidism and require TH replacement (3–6).

To avoid the ill effects of hypothyroidism on the body, some surgeons start TH supplementations immediately after surgery. However, long-term TH therapy may itself cause adverse effects such as hypocalcemia, myocardial damage and auricular fibrillation (7–9). Therefore it is important to precisely identify patients who are at risk for hypothyroidism after hemithyroidectomy, then give the TH supplementation therapy.

Known risk factors for TH replacement after hemithyroidectomy include elevated preoperative serum thyroid-stimulating hormone (TSH) level, presence of thyroid peroxidase antibody (TPOAb), and concomitant thyroiditis (5, 10–13). However, the predictive value of some other clinical factors remains unclear and controversial. The aims of this study were to 1) explore the incidence of hypothyroidism following hemithyroidectomy, 2) identify the risk factors for TH replacement after thyroid surgery, and 3) develop a binomial logistic-regression model for predicting the need for TH replacement after hemithyroidectomy. Surgeons can give patients preoperative counseling and postoperative guidance by using this nomogram. Based on the STROBE reporting checklists, we present this article.

Materials And Methods

Patient selection

The study population was selected from 1076 patients with benign thyroid disease who underwent hemithyroidectomy between January 2015 and January 2020 at Peking Union Medical College Hospital. All surgeries were performed by the same group of surgeons. Permission for clinical data collection was granted by the Peking Union Medical College Hospital Ethics Committee. The inclusion criteria were 1) normal normal preoperative serum TSH level, 2) age ≥ 18 years at the time of surgery. The exclusion criteria were 1) preexisting hyperthyroidism or hypothyroidism (n = 47), 2) less than 12 months follow-up (n = 456), 3) receipt of TH immediately after surgery (n = 152), 4) contralateral thyroid lobectomy performed after hemithyroidectomy (n = 6), 5) history of previous thyroid surgery (n = 18), or 6) history of thyroid cancer, cervical lymph node cancer, or pituitary disease (n = 19). A total of 378 patients met these criteria.

Pre- And Postoperative Assessment

The electronic medical records of the selected patients were accessed and data were collected on demographic characteristics, body mass index (BMI), admission diagnosis, surgery-related variables, pathological findings, and preoperative and postoperative thyroid function. Thyroid function were assessed via electrochemiluminescence immunoassay of serum TSH, TPOAb, thyroglobulin antibody (TgAb), free triiodothyronine (FT3), free thyroxine (FT4), triiodothyronine(T3), and thyroxine (T4) levels. At our institution, the reference ranges of TSH, TPOAb, TgAb, FT3, FT4, T3, and T4 are, respectively, 0.380-4.340 μIU/mL, < 34 IU/mL, < 115 IU/mL, 1.80-4.10 pg/mL, 0.81-1.89 ng/dL, 0.66-1.92 ng/mL, and 4.30-12.50 μg/dL.

Based on the results of postoperative thyroid function tests, patients were categorized into two groups: a postoperative euthyroid group (patients with both TSH and FT4 levels within reference ranges, n = 268) and a postoperative hypothyroid group (patients with subclinical and overt hypothyroidism, n = 110). Subclinical hypothyroidism was characterized by elevated serum TSH with normal FT4. Overt hypothyroidism was characterized by elevated serum TSH levels with low FT4 levels. According to the TH replacement following hemithyroidectomy, postoperative euthyroidism patients without TH replacement (n = 211) were compared to those who developed postoperative hypothyroidism with TH replacement (n = 56). Postoperative subclinical hypothyroidism patients without TH replacement were of two types: those who spontaneously reverted to euthyroidism (n = 36) and those with persistent subclinical hypothyroidism (n = 12).

Statistical analysis

Categorical variables were summarized as frequencies and percentages and analyzed by the chi-square test. Continuous variables were summarized as means ± standard deviations or medians and interquartile ranges and compared using one way analysis of variance (ANOVA) or the Kruskal–Wallis test. Receiver operating characteristic (ROC) curve analysis was used to identify the optimum cutoff value of preoperative serum TSH for predicting the probability of postoperative TH replacement. Binomial logistic regression was performed to evaluate the impact of each variable in risk of postoperative TH replacement. Variables associated with need for TH therapy (at significance level of $P < 0.25$) in univariate analysis were entered into multivariate analysis[8]; the odds ratios (OR) and 95% confidence intervals (CIs) were calculated. Two-sided $P < 0.05$ was considered statistically significant. The identified variables were used to construct a visual nomogram for predicting the probability of TH replacement after surgery. The accuracy of this model was proven by the Hosmer–Lemeshow test. Internal validation of the nomogram was performed using a corrected calibration curve within 1000 bootstrap samples. Harrell concordance index (C-index) was used to assess prediction performance and discrimination, with C-index close to 1 indication of good predictive accuracy. Statistical analysis was carried out using SPSS 25.0 (IBM Corp., Armonk, NY, USA) and R 4.0.3 (https://cran.r-project.org/).

Results

Incidence and characteristic of hypothyroidism following hemithyroidectomy

Of the identified 378 patients, 268 (70.9%) patients had postoperative euthyroidism, 110 (29.1%) developed postoperative hypothyroidism. It presents a comparison of the baseline characteristics of these two groups (Table 1). Compared to the euthyroidism group, the hypothyroidism group had significantly lower mean preoperative FT3 and FT4 level, higher mean TSH, higher proportion of patients with serum TSH > 2.172 μIU/mL (i.e., the TSH cutoff identified by ROC analysis, area under the curve = 0.682), higher proportion of patients positive for TPOAb, and higher proportion of patients with concurrent Hashimoto thyroiditis. Patients with persistent postoperative hypothyroidism were also significantly younger than those with postoperative euthyroidism. In univariate logistic regression analysis, preoperative serum TSH > 2.172 μIU/mL was significantly associated with likelihood of postoperative hypothyroidism (OR, 7.47; 95% CI, 4.43 to 12.62; $P < 0.001$). Other variables (age at operation, preoperative TPOAb positivity, concurrent Hashimoto thyroiditis, and preoperative FT3 and FT4 levels) were not associated with postoperative hypothyroidism (Table 2). In adjusted multivariate analysis, only high preoperative TSH (> 2.172 μIU/mL) was an independent predictor of postoperative hypothyroidism (OR, 8.02; 95% CI, 4.87 to 13.20; $P < 0.001$). The mean interval from surgery to the development of hypothyroidism was 3.47 ± 7.79 months (Fig. 1). While 88 (80%) patients developed hypothyroidism within 3 months after hemithyroidectomy, 5 (4.5%) patients manifested hypothyroidism > 12 months after surgery.

Table 1
Baseline characteristics of patients with postoperative euthyroidism and hypothyroidism

Characteristics	**Postoperative euthyroidism (n = 268)**	**Postoperative hypothyroidism (n = 110)**	***P*[a]**
Age at operation, y	48.68 ± 12.25	48.61 ± 10.91	0.018
BMI, kg/m^2	24.40 ± 3.15	24.19 ± 3.33	0.838
Sex			0.092
Male	76 (28.4)	22 (20.0)	
Female	192 (71.6)	88 (80.0)	
Family history of thyroid disease			0.741
No	251 (93.7)	102 (92.7)	
Yes	17 (6.3)	8 (7.3)	
Admission diagnosis			0.109
Unilateral nodule	144 (53.7)	69 (62.7)	
Bilateral nodules	124 (46.3)	41 (37.3)	
Preop TSH, μIU/mL			
Median (P_{25}, P_{75})	1.38 (0.98, 1.93)	2.57 (1.82, 3.74)	<0.001
≤2.172 μIU/mL	220 (82.1)	40 (36.4)	<0.001
>2.172 μIU/mL	48 (17.9)	70 (63.6)	
Preop FT3, pg/mL	3.13 (2.95, 3.35)	2.98 (2.86, 3.28)	0.014
Preop FT4, ng/dL	1.18 (1.09, 1.28)	1.14 (1.05, 1.26)	0.025
Preop T3, ng/mL	1.08 (0.97, 1.20)	1.06 (0.95, 1.18)	0.259
Preop T4, μg/dL	7.70 (6.92, 8.70)	7.69 (6.79, 8.74)	0.568
Preop TgAb			0.138
Negative	239 (89.2)	92 (83.6)	

BMI, body mass index; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

Data are presented as mean ± standard deviation, n (%), or median (P_{25}, P_{75}).

Characteristics	Postoperative euthyroidism (n = 268)	Postoperative hypothyroidism (n = 110)	P[a]
Positive	29 (10.8)	18 (16.4)	
Preop TPOAb			0.005
Negative	241 (89.9)	87 (79.1)	
Positive	27 (10.1)	23 (20.9)	
Operation type			0.290
Thyroid lobectomy	222 (82.8)	86 (78.2)	
Thyroid lobectomy with isthmectomy	46 (17.2)	24 (21.8)	
Side of lobectomy			0.159
Left	126 (47.0)	43 (39.1)	
Right	142 (53.0)	67 (60.9)	
Hashimoto thyroiditis			0.040
Absent	251 (93.7)	96 (87.3)	
Present	17 (6.3)	14 (12.7)	
BMI, body mass index; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.			
Data are presented as mean ± standard deviation, n (%), or median (P_{25}, P_{75}).			

Table 2
Univariate and multivariate analysis of risk factors for postoperative hypothyroidism

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at operation	1.00 (0.98-1.03)	0.77		
Preop TSH > 2.172 μIU/mL	7.47 (4.43-12.62)	<0.001	8.02 (4.87-13.20)	<0.001
Lower preop FT3	0.59 (1.20-2.45)	0.61		
Lower preop FT4	0.41 (0.07-2.35)	0.32		
Preop TPOAb positivity	1.32 (0.60-2.89)	0.49		
Hashimoto thyroiditis	1.07 (0.40-2.82)	0.90		

OR, odds ratio; CI, confidence interval; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TPOAb, thyroid peroxidase antibody.

Incidence And Risk Factors For Th Replacement Following Hemithyroidectomy

Of 110 postoperative hypothyroidism patients, 56 patients finally required TH replacement during the follow-up; thus, the incidence of TH replacement following hemithyroidectomy was 50.9%. Postoperative hypothyroidism patients with TH replacement were significantly younger than those who developed postoperative euthyroidism without TH replacement. The TH replacement group had a higher proportion of females, patients with unilateral thyroid nodule, patients with preoperative serum TSH levels > 2.172 μIU/mL, with right sided lobectomy, and positive for TgAb and TPOAb. The preoperative serum TSH was significantly higher and serum FT3, FT4, and T4 significantly lower in patients who received TH replacement than in those who did not receive TH replacement (all $P < 0.05$; Table 3).

Table 3
Characteristics of postoperative euthyroidism patients without TH replacement and postoperative hypothyroidism patients with TH replacement

Characteristics	**Postoperative-euthyroidism patients without TH replacement (n = 211)**	**Postoperative-hypothyroidism patients with TH replacement (n = 56)**	***P*[a]**
Age at operation, y	49.59 ± 12.39	47.13 ± 9.80	0.006
BMI, kg/m^2	24.61 ± 3.10	24.29 ± 3.61	0.264
Sex			0.024
Male	66 (31.3)	9 (16.1)	
Female	145 (68.7)	47 (83.9)	
Family history of thyroid disease			0.298
No	200 (94.8)	51 (91.1)	
Yes	11 (5.2)	5 (8.9)	
Admission diagnosis			0.022
Unilateral nodule	107 (50.7)	38 (67.9)	
Bilateral nodules	104 (49.3)	18 (32.1)	
Preop TSH, μIU/mL			
Median (P_{25}, P_{75})	1.29 (0.95, 1.79)	2.87 (1.84, 3.90)	<0.001
≤2.172 μIU/mL	184 (87.2)	17 (30.4)	<0.001
>2.172 μIU/mL	27 (12.8)	39 (69.6)	
Preop FT3, g/mL	3.13 (2.94, 3.32)	2.97 (2.85, 3.26)	0.015
Pre FT4, ng/dL	1.18 (1.09, 1.29)	1.10 (1.03, 1.26)	0.006
Preop T3, ng/mL	1.08 (0.97, 1.21)	1.05 (0.96, 1.18)	0.265
Preop T4, μg/dL	7.70 (6.99, 8.80)	7.20 (6.33, 8.38)	0.044
Preop TgAb			0.038
Negative	188 (89.1)	44 (78.6)	

BMI, body mass index; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

Data are presented as mean ± standard deviation, n (%), or median (P_{25}, P_{75}).

Characteristics	Postoperative- euthyroidism patients without TH replacement (n = 211)	Postoperative- hypothyroidism patients with TH replacement (n = 56)	P^a
Positive	23 (10.9)	12 (21.4)	
Preop TPOAb			0.001
Negative	192 (91.0)	42 (75.0)	
Positive	19 (9.0)	14 (25.0)	
Operation type			0.103
Thyroid lobectomy	181 (85.8)	43 (76.8)	
Thyroid lobectomy with isthmusectomy	30 (14.2)	13 (23.2)	
Side of lobectomy			0.041
Left	100 (47.4)	18 (32.1)	
Right	111 (52.6)	38 (67.9)	
Hashimoto thyroiditis			0.134
Absent	200 (94.8)	50 (89.3)	
Present	11 (5.2)	6 (10.7)	

BMI, body mass index; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

Data are presented as mean ± standard deviation, n (%), or median (P_{25}, P_{75}).

It presents the results of univariate and multivariate analyses (Table 4). In univariate analysis, the factors associated with TH replacement included admission diagnosis of unilateral thyroid nodule (P = 0.02), preoperative serum TSH > 2.172 μIU/mL (P < 0.001), low preoperative T4 (P = 0.11), preoperative TgAb positivity (P = 0.22), and right-side lobectomy (P = 0.14) were found to be linked with TH replacement following HT. Age at operation, sex, and preoperative FT3, FT4, and TPOAb were not associated with TH replacement (P = 0.64, P = 0.27, P = 0.75, P = 0.49, P = 0.53, respectively). In adjusted multivariate analysis, only two variables were independent predictors of TH replacement, i.e., admission diagnosis of unilateral thyroid nodule (OR = 2.77; 95% CI: 1.27-6.04, P = 0.01) and preoperative serum TSH >2.172 μIU/mL (OR, 16.30; 95% CI, 7.77 to 34.18; P < 0.001).

Table 4
Univariate and multivariate analyses of the risk factors for TH replacement following hemithyroidectomy

Variable	Univariate		Multivariate	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age at operation	0.99 (0.96-1.03)	0.64		
Female	1.83 (0.63-5.31)	0.27		
Unilateral thyroid nodule	2.76 (1.21-6.28)	0.02	2.77 (1.27-6.04)	0.01
Preop TSH > 2.172 μIU/mL	16.80 (7.48-37.74)	<0.001	16.30 (7.77-34.18)	<0.001
Lower preop FT3	1.23 (0.35-4.31)	0.75		
Lower preop FT4	2.98 (0.13-66.75)	0.49		
Lower preop T4	0.79 (0.59-1.06)	0.11	0.82 (0.64-1.06)	0.83
Preop TgAb positivity	2.06 (0.65-6.56)	0.22	0.97 (2.52-6.60)	0.06
Preop TPOAb positivity	1.43 (0.47-4.35)	0.53		
Right-side lobectomy	1.80 (0.83-3.92)	0.14	1.72 (0.80-3.68)	0.16

Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; OR, odds ratio; CI, confidence interval.

Some patients with subclinical hypothyroidism spontaneously reverted to euthyroidism without TH replacement. Hence, patients with subclinical hypothyroidism who did not receive TH replacement were divided into a persistent subclinical hypothyroidism group (n = 36) and a reverted to euthyroidism group (n = 12). Table 5 presents a comparison of these two groups. Significant predictors of reversion to euthyroidism after developing subclinical hypothyroidism were not identified.

Table 5
Characteristics of patients with subclinical hypothyroidism not receiving TH replacement after surgery

Characteristics	Persistent subclinical hypothyroidism (n = 36)	Spontaneously reverted to euthyroidism (n = 12)	*P*
Age at operation, y	50.33 ± 11.90	49.42 ± 14.65	0.464
BMI, kg/m^2	24.04 ± 2.85	24.39 ± 3.21	0.451
Sex			0.322
Male	10 (27.8)	1 (8.3)	
Female	26 (72.2)	11 (91.7)	
Family history of thyroid disease			>0.99
No	34 (94.4)	11 (91.7)	
Yes	2 (5.6)	1 (8.3)	
Admission diagnosis			>0.99
Unilateral nodule	21 (58.3)	7 (58.3)	
Bilateral nodules	15 (41.7)	5 (41.7)	
Preop TSH level, μIU/mL			>0.99
≤2.172 μIU/mL	18 (50.0)	6 (50.0)	
>2.172 μIU/mL	18 (50.0)	6 (50.0)	
Preop FT3, pg/mL	3.08 (2.93, 3.42)	2.91 (2.75, 3.12)	0.067
Preop FT4, ng/dL	1.19 (1.12, 1.27)	1.22 (1.07, 1.29)	0.153
Preop T3, ng/mL	1.13 (0.94, 1.20)	1.00 (0.98, 1.08)	0.721
Preop T4, μg/dL	8.21 (7.47, 8.90)	7.84 (7.15, 9.30)	0.592
Preop TgAb			0.546
Negative	34 (94.4)	10 (83.3)	
Positive	2 (5.6)	2 (16.7)	
Preop TPOAb			>0.99

BMI, body mass index; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

Data are presented as mean ± standard deviation, n (%), or median (P_{25}, P_{75}).

Characteristics	Persistent subclinical hypothyroidism (n = 36)	Spontaneously reverted to euthyroidism (n = 12)	*P*
Negative	32 (88.9)	10 (83.3)	
Positive	4 (11.1)	2 (16.7)	
Operation type			0.655
Thyroid lobectomy	29 (80.6)	11 (91.7)	
Thyroid lobectomy with isthmusectomy	7 (19.4)	1 (8.3)	
Side of lobectomy			>0.99
Left	15 (41.7)	5 (41.7)	
Right	21 (58.3)	7 (58.3)	
Hashimoto thyroiditis			>0.99
Absent	32 (88.9)	11 (91.7)	
Present	4 (11.1)	1 (8.3)	
BMI, body mass index; Preop, preoperative; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.			
Data are presented as mean ± standard deviation, n (%), or median (P_{25}, P_{75}).			

Nomogram Development And Validation

A binomial logistic-regression model was built using six risk factors identified by univariate and multivariate analysis: i.e., sex, admission diagnosis, side of lobectomy, preoperative TSH and T4 levels, and TgAb positivity (Fig. 2A), and visualized as a nomogram for predicting the probability of TH replacement after hemithyroidectomy. The risk of medication probability predicted by this nomogram model ranged from 0.010 to 0.999. The consistency of the model was confirmed by the Hosmer–Lemeshow goodness-of-fit test ($\chi2$ = 4.016, df = 8, P = 0.856). The calibration curves showed a largely perfect agreement between nomogram-predicted outcomes and actual outcomes (Fig. 2B). The model performed well, with Harrel's C-index of 0.85. For clinical convenience, we uploaded an online-program using the "DynNom" package of R; it is available at https://liuruisurgeon.shinyapps.io/THRgrade/. After determining the parameters, the probability of TH replacement can be obtained by clicking the "predict" button (Fig. 3).

Discussion

The overall incidence of hypothyroidism after surgery was 29.1% in our cohort, and almost half of them received postoperative TH replacement, which was consistent with earlier studies varied from 11–45% (4, 5, 10, 14). The mean interval from surgery to the development of hypothyroidism was 3.47 months in our study. Most cases of hypothyroidism occurred in the early follow-up period; 80% of patients had developed hypothyroidism within 3 months, and about 90% within 9 months. Thus, the findings suggested that monitoring period of thyroid function for at least 9 months after hemithyroidectomy would ensure that at least 90% of hypothyroidism cases were detected. In a retrospective analysis of 405 patients undergoing hemithyroidectomy, Ahn et al. (4) reported similar results. In our study, about 5% of patients were diagnosed with hypothyroidism, the authors therefore recommended prolonged follow-up of thyroid function, particularly for patients with high risk of hypothyroidism.

Multiple prior studies have found that elevated preoperative serum TSH, presence of TPOAb, and concomitant thyroiditis are predictors of need for postoperative TH replacement (2, 5, 10, 11, 15, 16). In our study, besides elevated preoperative serum TSH, admission diagnosis of unilateral thyroid nodule was also found to be predictor of TH replacement therapy. Consistent with previous studies, preoperative TSH level had the strongest predictive value (highest odds ratio) (2, 16). In our opinion, higher preoperative TSH levels indicated lower reserved thyroid function and, therefore, greater likelihood of developing hypothyroidism after surgery. ROC analysis identified preoperative TSH 2.172 μIU/mL as the best cutoff value for identifying patients at high risk of developing postoperative hypothyroidism. Hypothyroidism developed in 63.6% of patients with TSH >2.172 μIU/mL vs. 36.4% of patients with TSH ≤ 2.172 μIU/mL ($P < 0.001$). The cut-off value identified in previous studies ranged from 1.4 to 2.5 mIU/L (2, 16, 17).

A surprising finding was that unilateral thyroid nodule was an independent predictor of postoperative TH replacement. This finding has not been reported before. In a study of 150 patients undergoing hemithyroidectomy, Lang et al. (18) found that fewer number of ipsilateral nodules was associated with increased risk for hypothyroidism after surgery. This is, to some extent, similar to our finding. Further research is needed to clarify the link between unilateral thyroid nodule and postoperative hypothyroidism.

In this study, we separately evaluated patients with subclinical hypothyroidism; this subgroup has not been adequately assessed in previous studies (19, 20). In our sample, 25% of patients with subclinical hypothyroidism following hemithyroidectomy reverted to euthyroidism without TH replacement. However, statistically significant predictors of reversion to euthyroid state were not identified, probably because our sample size was small. Buehler et al. (10) found that nearly half of their patients with subclinical hypothyroidism recovered to normal thyroid function within a 5-year follow-up period. The larger proportion identified probably due to the longer follow-up and included observation of thyroid cancer patients. These findings suggested that all patients who develop postoperative subclinical hypothyroidism could not need immediate TH replacement.

A binomial logistic-regression model was built using the variables significantly associated with TH replacement, and visualized as a nomogram for predicting the probability of TH replacement after surgery. Multiple previous studies have proved that the nomogram has better predictive performance (21, 22). To our knowledge, this is the first report of a nomogram for predicting benign thyroid disease. Our model was shown to be reliable, with a good C-index. The ability to predict TH replacement can be useful considering the side effects of TH supplementation and, currently, the difficulty in following up patients due to the COVID-19 pandemic (23).

Our study has several limitations. First, although unilateral thyroid nodule was identified as an independent risk factor for TH replacement, we did not measure the number and volume of thyroid nodules by ultrasonography. The reason why presence of the contralateral thyroid nodules relatively acts as a protective factor remains unexplained. Second, we did not quantitatively assess chronic lymphocytic infiltration by histopathology which has been previously identified as a potential predictor of TH replacement. Third, this was a retrospective single-center study, and therefore information bias and selection bias cannot be ruled out. Fourth, external validation of the logistic model was not performed. Further studies are needed for confirmation.

Conclusion

In summary, approximately one-third of patients undergoing hemithyroidectomy may develop hypothyroidism, and of these almost half will require TH replacement. Elevated preoperative serum TSH level and admission diagnosis of unilateral thyroid nodule appear to be independent predictors of need for TH replacement following hemithyroidectomy. The constructed visual nomogram is a simple and objective tool that can predict the probability of need for TH replacement following hemithyroidectomy and help identify patients who need close follow-up after thyroid surgery.

Declarations

Author contributions (I) Conception and design: Z Cao, X Xu; (II) Administrative support: X Xu, Z Liu; (III) Provision of study materials or patients: X Xu, X Li, Z Liu; (IV) Collection and assembly of data: Z Cao, R Liu, M Wu; (V) Data analysis and interpretation: Z Cao, R Liu, M Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Availability of data and material The datasets in this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of the Peking Union Medical College Hospital and individual consent for this retrospective analysis was waived. All the procedures being performed were part of the routine care.

Informed consent Not applicable.

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Figures

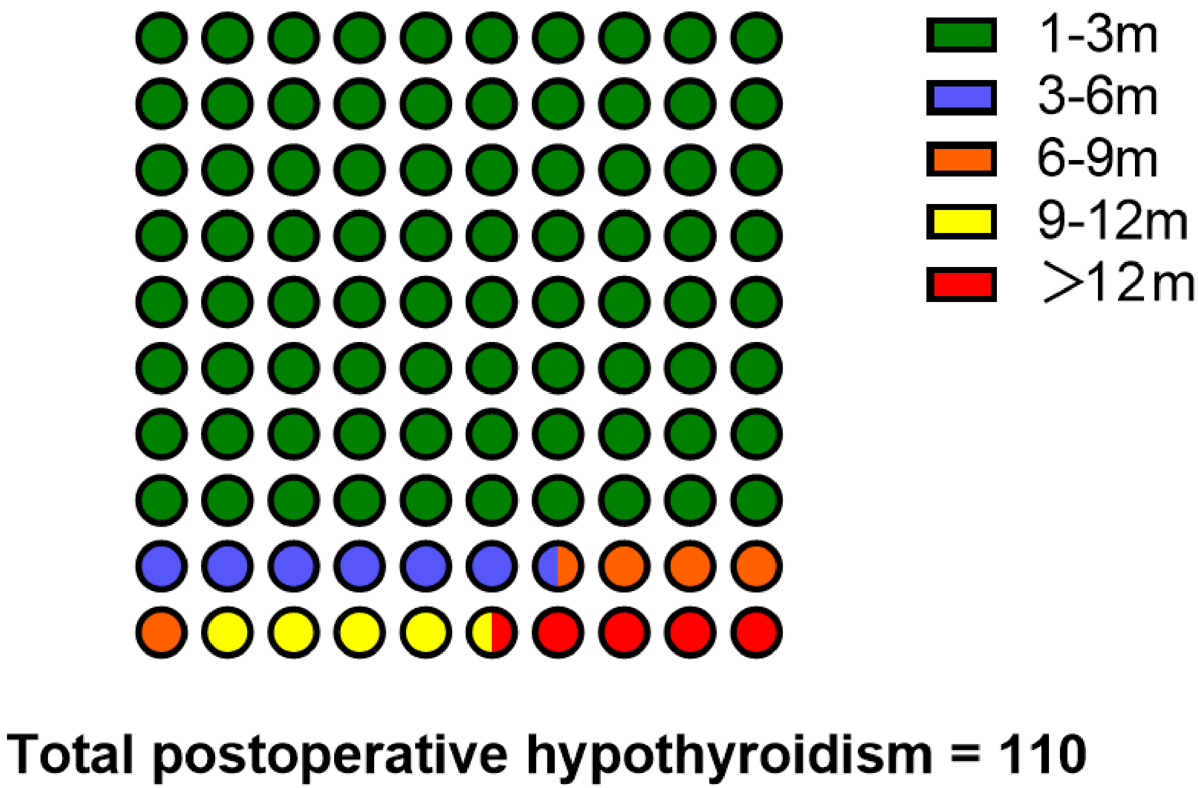

Figure 1

Time interval from hemithyroidectomy to the development of hypothyroidism

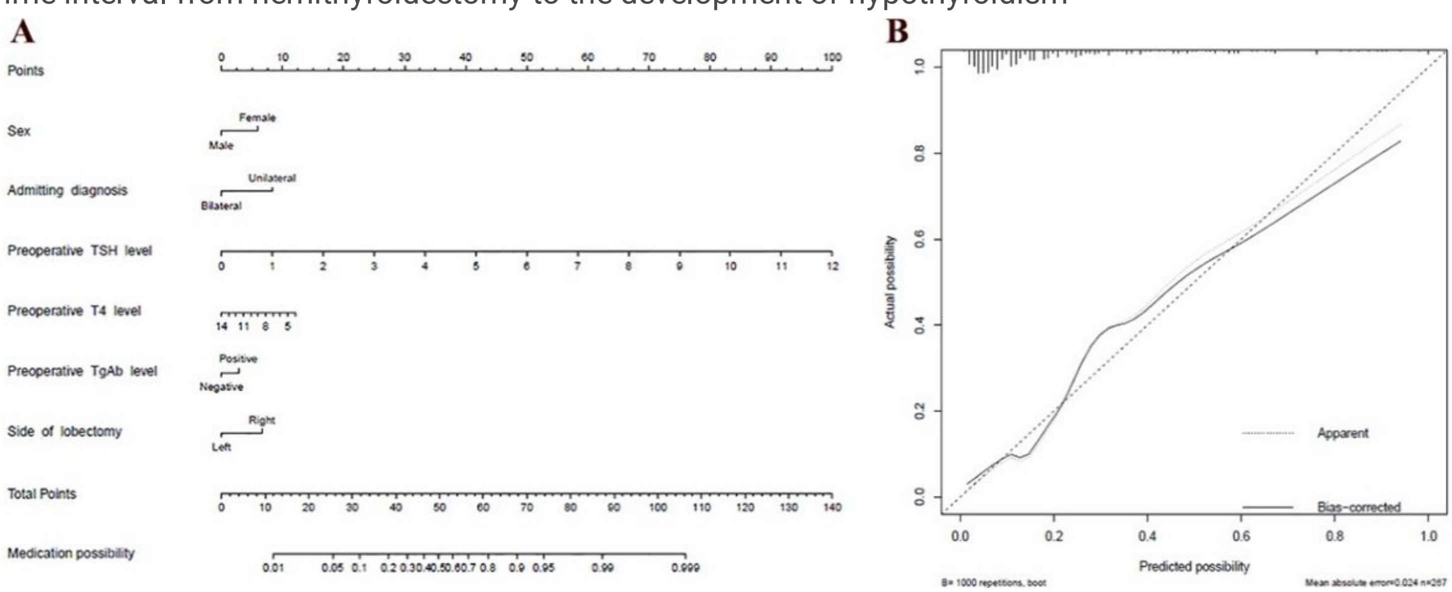

Figure 2

A binomial logistic-regression model (A) Nomogram for predicting the probability of thyroid hormone replacement following hemithyroidectomy and (B) calibration curves of the nomogram. The 45° dashed line represents the ideal predictions (ideal line). The solid line is a bias-corrected curve. The dotted line is the nomogram probability

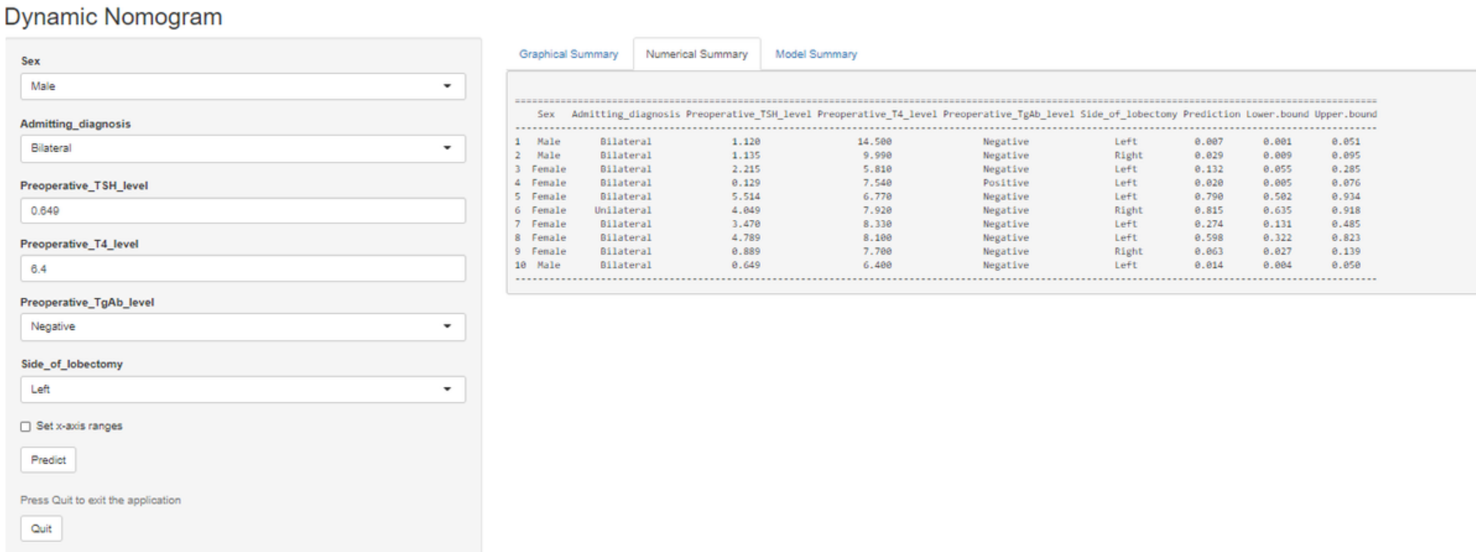

Figure 3

The online program for predicting the probability of thyroid hormone replacement following hemithyroidectomy is available at https://liuruisurgeon.shinyapps.io/THRgrade/