ORIGINAL ARTICLE

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

Zhen Cao[1] · Rui Liu[1] · Mengwei Wu[1] · Xiequn Xu[1] · Ziwen Liu [1]

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 ($P = 0.503$), and predictive ability of the nomogram was satisfactory with a C-index of 0.833.

Conclusions 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.

Keywords Hemithyroidectomy · Thyroid hormone replacement · Thyroid-stimulating hormone (TSH) · Nomogram

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 [4–6].

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

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These authors contributed equally: Zhen Cao, Rui Liu

✉ Xiequn Xu
  xxq75@163.com

✉ Ziwen Liu
  liuziwen@pumch.cn

[1] Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 100730 Beijing, People's Republic of China

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 thyroid surgeries were performed by the same group of surgeons at one institution. The procedure performed was confirmed from the operative note. A hemithyroidectomy was defined as complete removal of unilateral thyroid lobe and preservation of the contralateral lobe with or without isthmusectomy. The preserved isthmus was sewn using 2-0 polypropylene sutures. The types of hemithyroidectomy performed included conventional open or endoscopic procedure based on patient preference. Permission for clinical data collection was granted by the Peking Union Medical College Hospital Ethics Committee. The inclusion criteria were (1) 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 tests (TFT) 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. Normal thyroid function was confirmed on the TFT before surgery. During the follow-up period, patients underwent thyroid function assessments at 1, 3, 6, and 12 months postoperatively, then every six months after that. However, when patients complained the clinical symptoms related to thyroid dysfunction or had suspicious TFT results, TFTs were performed at any time. The presence of hypothyroidism symptoms included a puffy face, fatigue, and weight gain. The development of hypothyroidism, type of hypothyroidism, TSH level at diagnosis, the interval between operation and the development of hypothyroidism, spontaneous recovery from hypothyroidism, and the use of TH replacement were recorded.

Based on the results of postoperative TFT, 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. Of the 110 postoperative hypothyroid patients, 56 patients received TH replacement, and 54 patients were not medicated due to no obvious discomfortable symptoms. 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 ($n = 56$). Of the 54 patients without TH replacement, 48 patients were diagnosed with subclinical hypothyroidism and six patients were diagnosed with overt hypothyroidism. 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 the significance level of $P <$ 0.1) in univariate analysis were entered into multivariate analysis; 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) and ROC curves 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, 95%CI, 0.621–0.742; sensitivity, 54.0%; specificity, 78.5%; Fig. 1), 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/

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)	
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)	

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

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

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. 2). While 88

(80%) patients developed hypothyroidism within 3 months after hemithyroidectomy, 5 (4.5%) patients manifested hypothyroidism >12 months after surgery.

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%. The association between the characteristic of postoperative euthyroidism patients without TH replacement and postoperative hypothyroidism patients with TH replacement is shown in Table 3. 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 $P < 0.05$).

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 ($P = 0.02$), Female ($P = 0.03$), preoperative serum TSH > 2.172 µIU/mL ($P < 0.001$), low preoperative FT3, FT4 and T4 ($P = 0.04$, $P = 0.01$, $P = 0.03$, respectively), preoperative TgAb and TPOAb positivity ($P = 0.09$, $P = 0.01$, respectively), and right-side lobectomy ($P = 0.07$) were found to be linked with TH replacement following HT. Age at operation, and preoperative T3, thyroid lobectomy with isthmusectomy and present of Hashimoto thyroiditis were not associated with TH replacement ($P = 0.18$, $P = 0.16$, $P = 0.11$, $P = 0.30$, respectively). In adjusted multivariate analysis, only two variables were independent predictors of TH replacement,
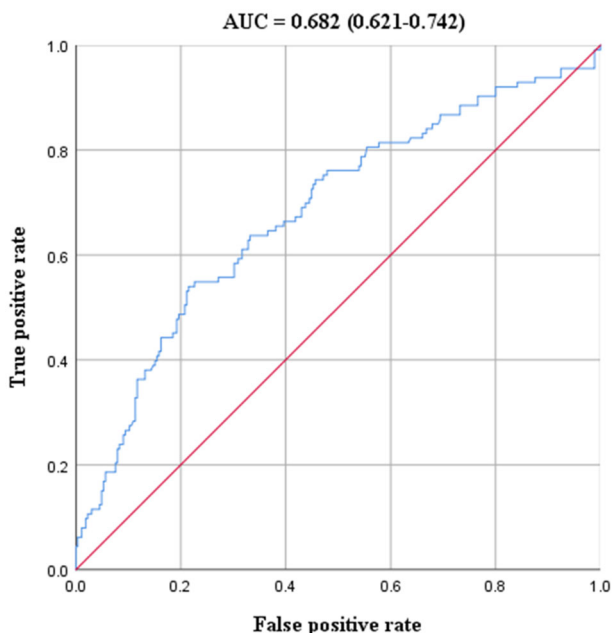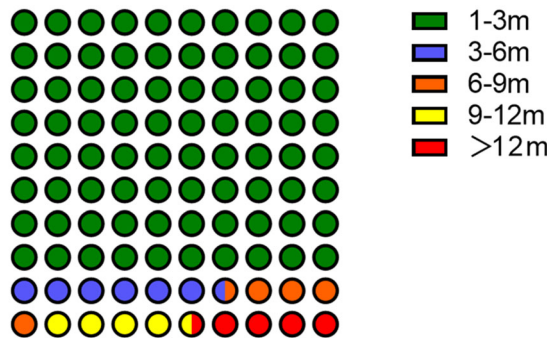

Fig. 1 The ROC curve of TSH cutoff value. The area under the ROC curve (AUC) is 0.682, 95%CI, 0.621–0.742. ROC receiver operating characteristic, AUC area under curve

Fig. 2 Time interval from hemithyroidectomy to the development of hypothyroidism

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

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)	
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)	

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

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

i.e., admission diagnosis of unilateral thyroid nodule (OR = 2.81; 95% CI: 1.26 to 6.26, $P = 0.01$) and preoperative serum TSH > 2.172 μIU/mL (OR, 17.94; 95% CI, 7.97–40.39; $P < 0.001$).

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.

Nomogram development and validation

Based on the abovementioned nine factors enrolled into multivariate analysis, we built a logistic regression model and visualized it into a nomogram. However, the length of three factors including preoperative FT3, TgAb and side of lobectomy were too short, and when excluded, the predictive ability of the model didn't decline at a significantly level (C-index was 0.8334 before excluded and 0.8333 after). Therefore, a binomial logistic-regression model was built using six risk factors identified by univariate and multivariate analysis: i.e., sex, admission diagnosis, preoperative TSH, FT4 and T4 levels, and TPOAb positivity (Fig. 3A), 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 ($\chi2 = 7.313$, df = 8, $P = 0.503$). The calibration curves showed a largely perfect agreement between nomogram-predicted outcomes and actual outcomes (Fig. 3B). The model performed well, with Harrel's C-index of 0.833 and the area under curve (AUC) was 0.833 (95%CI, 0.768–0.898) (Fig. 3C). Nomograms show the likelihood of TH replacement after hemithyroidectomy as a percentage, and we assigned a Youden-derived cutoff value to the nomogram. The optimal cutoff value was 39.371 (sensitivity, 73.2%; specificity, 85.8%; negative predictive value, 92.3%; positive predictive value, 57.7%). For clinical convenience, we uploaded an online-program using the "DynNom" package of R (https://cran.r-project.org/web/packages/DynNom/index.html); it is available at https://liuruisurgeon.shinyapps.io/TH_replacement/. After determining the parameters, the probability of TH replacement can be obtained by clicking the "predict" button (Fig. 4).

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	0.98 (0.96–1.00)	0.18		
Female	2.38 (1.10–5.14)	0.03	1.83 (0.63–5.32)	0.27
Unilateral thyroid nodule	2.05 (1.10–3.82)	0.02	2.81 (1.26–6.26)	0.01
Preop TSH > 2.172 µIU/mL	17.04 (8.41–34.54)	<0.001	17.94 (7.97–40.39)	<0.001
Lower preop FT3	0.37 (0.14–0.94)	0.04	1.22 (0.35–4.27)	0.76
Lower preop FT4	0.04 (0.01–0.31)	0.01	3.01 (0.14–65.7)	0.48
Lower preop T3	0.27 (0.04–1.67)	0.16		
Lower preop T4	0.79 (0.64–0.98)	0.03	0.77 (0.58–1.03)	0.77
Preop TgAb positivity	1.99 (0.91–4.40)	0.09	1.87 (0.58–6.08)	0.30
Preop TPOAb positivity	3.06 (1.40–6.66)	0.01	1.28 (0.42–3.96)	0.67
Thyroid lobectomy with isthmusectomy	1.83 (0.88–3.78)	0.11		
Right-side lobectomy	1.75 (0.95–3.25)	0.07	1.69 (0.78–3.66)	0.19
Present of Hashimoto thyroiditis	1.78 (0.59–5.36)	0.30		

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

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 to 45% [5, 6, 10, 11, 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, nearly 5% of patients were diagnosed with postoperative hypothyroidism beyond 12 months. Therefore, we 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) [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 [16, 17].

A surprising finding was that unilateral thyroid nodule was an independent predictor of postoperative TH replacement. This finding is different from what surgeons usually think and has not been accurately 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. We boldly wondered if there were bilateral nodules that increased compensatory thyroid function. Contralateral thyroid nodules after hemithyroidectomy boosted thyroid function. Based on more clinical studies, 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.

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
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)	

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

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

Buehler et al. [10] found that nearly half of their patients with subclinical hypothyroidism recovered to normal thyroid fu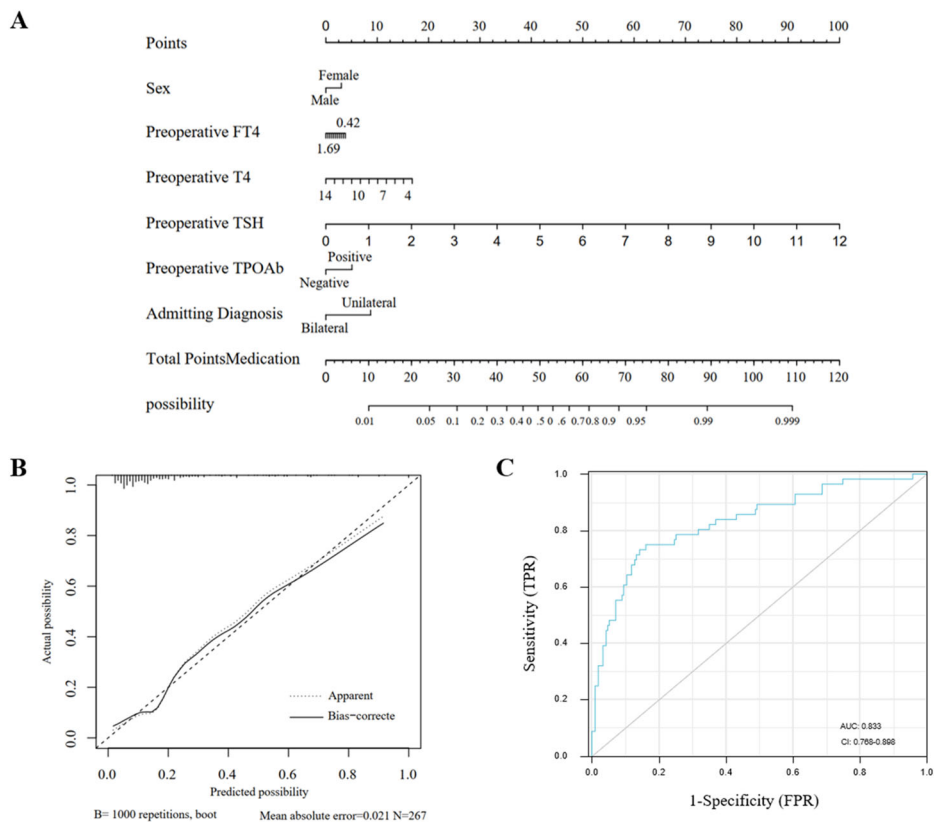nction within a 5-year follow-up period. The larger proportion identified probably due to the longer follow-up and included observation of thyroid cancer patients. These findings suggested that all patients who develop postoperative subclinical hypothyroidism could not need immediate TH replacement.

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 [21–23]. 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. According to previous study, an AUC value greater than 0.7 has superior accuracy, indicating good discrimination. With an optimal cutoff value of 39.371, the nomogram yielded 73.2% sensitivity, 85.8% specificity. Therefore, patients with a total point value of more than 39.371 are at high risk for TH replacement. However, close observation with TFT and follow-up are recommended for patients with a total point value of less than 39.371. Thus, 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 [24].

Several studies reported that an elevated TSH level were associated with a higher incidence of thyroid carcinoma and advanced diseases. Therefore, some surgeons believed that thyroid cancer patients should be supplemented with levothyroxine to suppress TSH to prevent possible tumor recurrence or progression. They focused on patients with thyroid carcinoma to explore the risk factors and determined the optimum suppressed TSH level to improve the prognosis [25–27]. Nevertheless, some surgeons considered that there was little evidence to guide TSH suppression therapy in low-risk patients who have undergone lobectomy [4, 17]. They evaluated the risk factors of hypothyroidism following hemithyroidectomy and focused on patients with benign thyroid disease and thyroid carcinoma. In our study, the identified 378 patients underwent hemithyroidectomy for benign thyroid disease. Since TH replacement were often given in patients with postoperative hypothyroidism following hemithyroidectomy rather than suppressive therapy, we merely included patients with benign thyroid disease to analyze and excluded ones with thyroid cancer.

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

Fig. 3 A binomial logistic-regression model (**A**) Nomogram for predicting the probability of thyroid hormone replacement following hemithyroidectomy, (**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 and (**C**) the ROC curve of nomograms for predicting the probability of TH replacement. The area under the ROC curve (AUC) is 0.833, 95%CI 0.768–0.898. ROC receiver operating characteristic, AUC area under curve

Fig. 4 The online program for predicting the probability of thyroid hormone replacement following hemithyroidectomy is available at https://liuruisurgeon.shinyapps.io/TH_replacement/

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.

Data availability

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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.

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