

# Measurement of serum intact parathyroid hormone concentration 1 day after total thyroidectomy to assess risk of permanent hypoparathyroidism

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## Abstract

**Objective:** This study was performed to assess the clinical value of measuring the intact parathyroid hormone (iPTH) concentration 1 day after total thyroidectomy to estimate the occurrence of permanent hypoparathyroidism (pHPP).

**Methods:** Data of 546 patients who underwent total thyroidectomy from February 2008 to December 2018 were retrospectively analyzed. Calcium and iPTH concentrations were collected preoperatively and at 1 day and 6 months postoperatively. Logistic regression was used to analyze the correlation between clinical indexes and postoperative pHPP.

**Results:** Of the 546 patients, 22 (4.03%) developed pHPP. Multivariate analysis showed that the iPTH and serum calcium concentrations measured 1 day after surgery were independent predictors of the risk of pHPP. An iPTH concentration of 5.51 pg/mL measured 1 day postoperatively was used as the cut-off value, and the area under the curve was 0.956. The risk of pHPP was identified with a sensitivity of 100%, specificity of 85.1%, positive predictive value of 22%, and negative predictive value of 100%.

**Conclusions:** The iPTH concentration measured 1 day after total thyroidectomy is closely related to the occurrence of pHPP postoperatively and is an independent predictive risk factor. The postoperative iPTH concentration can be helpful in identifying patients at risk for developing pHPP.

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## Keywords

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## Introduction

Although the incidence of permanent hypoparathyroidism (pHPP) after thyroidectomy is low, it is a serious complication after thyroid surgery with an incidence rate of 1% to 7%.<sup>1</sup> Measurement of the postoperative calcium and/or vitamin D concentration is a reasonable method to predict the occurrence of pHPP and is conducive to determining early and safe discharge of patients, reducing perioperative complications, and avoiding excessive treatment during hospitalization.<sup>2–5</sup> In the past, the postoperative serum calcium concentration was used for assessment, but postoperative hypocalcemia is influenced by many factors.<sup>6</sup> Thus, its accuracy as a predictive indicator has been disputed. Serum intact parathyroid hormone (iPTH) is characterized by a short half-life (3–5 minutes), and the serum calcium status can be evaluated according to the early postoperative iPTH concentration.<sup>7–9</sup> However, although the iPTH concentration has been measured as a reference, no clinical agreement has been reached on its cut-off value. Many studies have shown that a low iPTH concentration in the early postoperative period is the most reliable risk indicator for hypocalcemia after thyroidectomy. In view of this situation, the present study was performed to analyze the correlation between the occurrence of pHPP and the iPTH and serum calcium concentrations measured 1 day after total thyroidectomy among patients in our hospital and to evaluate the predictive value of the iPTH concentration.

These data will provide a reference for clinical screening and accurate treatment of high-risk patients who may develop pHPP after total thyroidectomy.

## Materials and methods

### Patient selection

We retrospectively reviewed consecutive patients who underwent surgical treatment of benign and malignant thyroid diseases in the Department of General Surgery, Beijing Chaoyang Hospital affiliated to Capital Medical University, Beijing, China from February 2008 to December 2018. The inclusion criteria were performance of total thyroidectomy for treatment of benign or malignant thyroid disease or on a prophylactic basis because of a *BRAF* mutation, monitoring of the serum calcium and iPTH concentrations 1 day postoperatively, and complete postoperative follow-up. The exclusion criteria were one-sided thyroid gland lobectomy or total excision, incomplete postoperative serum calcium and iPTH monitoring data, interruption of postoperative follow-up, and known parathyroid or metabolic bone disease, renal failure, previous neck surgery, or calcium and/or vitamin D supplementation. This study was conducted in accordance with the latest version of the Declaration of Helsinki of the World Medical Association. The study was approved by the Ethics Committee of Beijing Chaoyang Hospital. Verbal consent was obtained from the patients after they had received

an explanation of the procedure and potential risks encountered. Written informed consent was subsequently obtained using a form approved by the Ethics Committee and is available upon request.

### *Surgical procedure*

All operations were performed by four thyroid specialists in the department of general surgery. According to the institutional protocol, the surgical resection range was determined by the preoperative pathological diagnosis. All patients with thyroid cancer underwent total thyroidectomy plus central compartment lymphadenectomy of the affected side, and patients with multinodular thyroid goiter or thyroid follicular tumor underwent total thyroidectomy. The patients underwent general anesthesia in the supine position. Total thyroidectomy was then performed as follows. After the thyroid gland had been completely exposed, the upper pole of the thyroid gland was cut off with an ultrasonic knife. The dorsal side of the thyroid gland was separated near the inferior corner of the thyroid cartilage, and the parathyroid gland was preserved in situ by fine capsule dissection. If the parathyroid gland was mistakenly cut, the cut parathyroid gland was immediately transplanted into the sternocleidomastoid muscle. Another method of parathyroid autotransplantation was slicing of the gland into 0.5- to 1.0-mm pieces. The slices were implanted into two or three small pockets fashioned in the subcutaneous tissue of the non-dominant forearm through 2- to 3-mm skin incisions.<sup>10</sup> This procedure required that the venipuncture for measurement of the serum PTH concentration be placed in the forearm without reimplantation. During surgery, the superior parathyroid gland located behind the upper pole of the thyroid was carefully identified, cautiously protected, and

separated from the thyroid gland. Before treatment of the thyroid gland inferior pole vessels, the inferior parathyroid gland located on the dorsal side of the inferior pole of the thyroid gland was identified. The parathyroid gland and its nourishing vessels were attached to the capsule and separated laterally, and the thyroid gland was then lifted. After routine exposure of the recurrent laryngeal nerve, the whole thyroid gland was removed. For additional lymph node dissection in the central region of the neck, the parathyroid gland located at the inferior pole of the thyroid and its nourishing vessels were separated to the lateral side of the recurrent laryngeal nerve. After fully exposing the recurrent laryngeal nerve, the lymphatic fat tissues in the tracheoesophageal groove and at the front of the trachea were cleaned.

### *Perioperative management*

All patients with symptomatic or severe hypocalcemia, even if asymptomatic, were initially treated with intravenous administration of 10% calcium gluconate as a calcium supplement at a dose of 1 to 2 g/day until the blood calcium concentration reached exceeded 1.90 mmol/L or symptoms disappeared. For patients with an iPTH concentration of <15 pg/mL at 1 day after surgery, calcium (1–3 g/day) and 1,25-hydroxyvitamin D (0.25–0.5 µg/day) were orally administered. Patients with mild asymptomatic hypocalcemia and an iPTH concentration of >15 pg/mL did not need to receive calcium supplement therapy.

### *Laboratory examinations and definitions*

The blood calcium concentration was measured by conventional methods. The reference range of serum calcium was 2.13 to 2.65 mmol/L. The serum parathyroid hormone concentration was determined as iPTH, and the reference range was 15 to 65 pg/mL. iPTH was estimated using an

automated electrochemiluminescent immunoassay analyzer (Modular Analytics E170; Roche Diagnostic GmbH, Mannheim, Germany). The threshold detection level was 1.2 pg/mL. The serum calcium, phosphate, magnesium, and albumin concentrations were determined using an automatic analyzer (cobas c 711; Roche Diagnostics GmbH).

Hypocalcemia was defined as a blood calcium concentration of  $<2.00$  mmol/L. Mild hypocalcemia was defined as a blood calcium concentration of 1.90 to 2.00 mmol/L. Severe hypocalcemia was defined as a blood calcium concentration of  $<1.90$  mmol/L the presence of facial numbness, foot numbness, or other symptoms of hypocalcemia. Biochemical hypoparathyroidism is defined as a low iPTH level, below the lower limit of the laboratory standard (usually 15 pg/mL), accompanied by hypocalcemia. The reference range of the iPTH concentration varies depending upon the laboratory. Clinical hypoparathyroidism is defined as biochemical hypoparathyroidism accompanied by symptoms and/or signs of hypocalcemia.<sup>11-13</sup> pHPP was defined as the need for calcium and/or vitamin D supplementation at 6 months postoperatively to maintain a normal blood calcium concentration and was usually accompanied by a serum iPTH concentration of  $<15$  pg/mL.<sup>12</sup>

### *Follow-up method*

Follow-up mainly involved laboratory examinations. Signs and symptoms of an abnormal blood calcium concentration were also taken into account. The serum calcium and iPTH levels were recorded 1 day and 6 months after surgery. In patients with postoperative hypocalcemia, the blood calcium concentration was measured daily until a normal level was reached with calcium and vitamin D supplementation. Renal function and the alkaline phosphatase, albumin, phosphate, magnesium, and

vitamin D concentrations were recorded before and 6 months after surgery to exclude other diseases or confirm vitamin D deficiency. The patients were closely monitored postoperatively for any signs or symptoms of hypocalcemia. The blood calcium level was measured at regular outpatient reexaminations to check for signs and symptoms of hypocalcemia. All patients who could not stop taking calcium and/or vitamin D were followed up at 6 months postoperatively; the follow-up time was then extended by another 6 to 12 months, during which time the serum calcium and iPTH concentrations were monitored.

### *Statistical analysis*

The statistical analysis was performed using a commercially available software package (SPSS version 22.0 for Windows; IBM Corp., Armonk, NY, USA). Possible influencing factors were collected and recorded as follows: age, sex, preoperative diagnosis, surgical method, preoperative laboratory test results, and serum calcium and iPTH concentrations 1 day after surgery. Categorical variables are expressed as frequency and percentage, and measurement variables are expressed as mean  $\pm$  standard deviation. An independent-samples t test was used to compare the differences between the measurement data groups. To compare categorical variables, the chi-square test or Fisher's exact test was used as appropriate. Logistic regression was used to analyze the correlation between clinical parameters and postoperative pHPP. A two-sided P value of  $<0.05$  was considered statistically significant.

Receiver operating characteristic curve analysis was performed using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the serum calcium and iPTH concentrations were calculated by the

area under the curve (AUC) to find the threshold values for predicting pHPP. With respect to the accuracy of the diagnostic test with an appropriate reference provided, an AUC of 0.5 to 0.6 suggests poor accuracy of the diagnostic test, 0.6 to 0.7 suggests sufficient accuracy, 0.7 to 0.8 suggests good accuracy, 0.8 to 0.9 suggests very good accuracy, and  $>0.9$  suggests excellent accuracy.<sup>13</sup>

## Results

### *Patient characteristics*

Among 647 consecutive patients who underwent total thyroidectomy, 101 were excluded because of incomplete postoperative data and interruption of follow-up; therefore, 546 patients were included in the final analysis. The 546 patients comprised 158 men and 388 women with a mean age of  $50.9 \pm 13.2$  years (range, 19.0–79.2 years). The postoperative pathological diagnoses were thyroid nodular goiter ( $n = 123$ ), thyroid follicular tumor ( $n = 83$ ), and malignant tumor ( $n = 340$ ). The 340 malignant tumors comprised thyroid papillary carcinoma ( $n = 322$ ), thyroid follicular carcinoma ( $n = 12$ ), medullary carcinoma ( $n = 4$ ), and anaplastic carcinoma ( $n = 2$ ). Total thyroidectomy was performed in 230 patients, and total thyroidectomy plus central compartment lymphadenectomy was performed in 316 patients. The mean preoperative baseline iPTH concentration was  $38.9 \pm 13.7$  pg/mL (range, 13.2–73.1 pg/mL), and the mean preoperative baseline serum calcium concentration was  $2.23 \pm 0.093$  mmol/L (range, 1.95–2.47 mmol/L) (see Table 1).

### *Changes in serum calcium and iPTH concentrations 1 day postoperatively and development of pHPP 6 months postoperatively*

Within 24 hours after surgery, 203 (37.1%) patients had hypocalcemia; among these

**Table 1.** Patient characteristics ( $n = 546$ ).

Variable	
Sex	
Male	158 (28.9)
Female	388 (71.1)
Age, years	$50.9 \pm 13.2$
Preoperative diagnosis	
Thyroid nodular goiter	123 (22.5)
Thyroid follicular tumor	83 (15.2)
Malignant tumor	340 (62.3)
Thyroid papillary carcinoma	322 (94.7)
Thyroid follicular carcinoma	12 (3.5)
Thyroid medullary carcinoma	4 (1.2)
Thyroid anaplastic carcinoma	2 (0.6)
Surgical procedure	
Total thyroidectomy	230 (42.1)
Total thyroidectomy plus central dissection	316 (57.9)
Preoperative baseline iPTH concentration, pg/mL	$38.9 \pm 13.7$
Preoperative baseline calcium concentration, mmol/L	$2.23 \pm 0.093$

Data are expressed as number (percentage) or mean  $\pm$  standard deviation.

iPTH, intact parathyroid hormone.

patients, 47 (23.2%) had symptoms. Most patients had mild hypocalcemia. The iPTH concentration was low ( $<15$  pg/mL) in 37.7% (206/546) of patients 1 day after surgery; of these patients, 43.7% (90/206) had hypocalcemia. This incidence was significantly higher than the 4.1% (14/340) of patients with a normal iPTH concentration 1 day after surgery ( $P < 0.001$ ). One day after surgery, 46.3% (94/203) of the patients with hypocalcemia had a normal iPTH concentration, which was higher than the 28.3% (97/343) of patients with a normal blood calcium concentration ( $P < 0.001$ ). The mean blood calcium concentration of patients with normal iPTH was  $2.10 \pm 0.01$  mmol/L, while that of patients with

**Table 2.** Comparison of relevant factors between patients with normal and low serum calcium and iPTH concentrations 1 day after total thyroidectomy (n = 546).

Variable	Serum calcium			iPTH			
	Total	Normal (n = 343)	Low (n = 203)	P-value	Normal (n = 340)	Low (n = 206)	P-value
Sex				0.960			0.787
Female	388	244	144		243	145	
Male	158	99	59		97	61	
Age, years		51.2 ± 13.6	50.0 ± 12.3	0.307	50.6 ± 9.9	51.3 ± 9.5	0.454
Preoperative diagnosis				0.771			0.709
Thyroid nodular goiter	123	78	45		75	48	
Thyroid follicular tumor	83	53	30		49	34	
Thyroid carcinoma	340	212	128		216	124	
Surgical procedure				0.088			0.266
Total thyroidectomy plus central dissection	316	189	127		190	126	
Total thyroidectomy	230	154	76		150	80	
Preoperative laboratory data							
Calcium, mmol/L		2.23 ± 0.09	2.22 ± 0.09	0.952	2.27 ± 0.08	2.26 ± 0.09	0.888
25-hydroxyvitamin D3, ng/mL		21.82 ± 8.38	20.94 ± 7.71	0.221	20.47 ± 8.38	19.19 ± 7.96	0.079
Magnesium, mmol/L		0.87 ± 0.07	0.89 ± 0.30	0.224	0.88 ± 0.31	0.84 ± 0.25	0.070
Phosphate, mmol/L		1.16 ± 0.18	1.13 ± 0.22	0.096	1.16 ± 0.16	1.13 ± 0.26	0.114
Alkaline phosphatase, pg/mL		73.4 ± 23.7	71.2 ± 21.6	0.256	62.1 ± 23.1	65.1 ± 18.7	0.111
TSH, mIU/L		1.87 ± 1.01	1.91 ± 0.95	0.653	1.95 ± 1.04	2.09 ± 1.04	0.147
iPTH, pg/mL		38.8 ± 11.9	39.4 ± 11.1	0.586	37.34 ± 15.5	39.07 ± 10.4	0.119
24 hours postoperatively							
iPTH, pg/mL		24.37 ± 10.6	21.23 ± 10.6	0.001	26.72 ± 8.45	9.07 ± 3.38	<0.001
Calcium, mmol/L		2.16 ± 0.05	1.95 ± 0.05	<0.001	2.10 ± 0.01	1.89 ± 0.12	<0.001

Data are expressed as number or as mean ± standard deviation.

iPTH, intact parathyroid hormone; TSH, thyroid-stimulating hormone.

A P value of <0.05 was considered statistically significant.



low iPTH  $1.89 \pm 0.12$  mmol/L; the difference between the two groups was statistically significant ( $P < 0.001$ ) (Table 2).

At 6 months postoperatively, The iPTH concentration was still  $<15$  pg/mL in 22 patients, and they required oral calcium and vitamin D supplementation to maintain a normal blood calcium concentration. Therefore, the incidence of pHPP after total thyroidectomy was in 4.03% (22/546) of the total sample. Among the 340 patients with a normal iPTH concentration 1 day after surgery, the iPTH concentration was within the reference range at 6 months after surgery, and all 22 patients with pHPP were among those with a low iPTH concentration 1 day after surgery.

### *Analysis of risk factors for pHPP at 6 months after thyroidectomy*

A univariate analysis was conducted based on the possible risk factors associated with pHPP after thyroid surgery.<sup>11</sup> The results showed that a low iPTH concentration ( $P = 0.001$ ) and a low serum calcium concentration ( $P = 0.009$ ) 1 day after surgery were risk factors for pHPP, and a low vitamin D concentration was a potential risk factor (Table 3). These factors were included in the logistic regression model for the multivariate analysis. At 6 months after thyroid surgery, the patients were divided into those with pHPP ( $n = 22$ ) and those without pHPP ( $n = 524$ ). The results

**Table 3.** Univariate analysis of pHPP at 6 months after total thyroidectomy.

Variable	Total 546	No pHPP (n = 524)	pHPP (n = 22)	P
Age, years				0.795
<45	262	252 (48.1)	10 (45.5)	
$\geq 45$	284	272 (51.9)	12 (54.5)	
Sex				0.865
Male	92	88 (16.8)	4 (18.2)	
Female	454	436 (83.2)	18 (81.8)	
Surgery procedure				0.576
Total thyroidectomy plus central dissection	316	302 (57.6)	14 (63.6)	
Total thyroidectomy	230	222 (42.4)	8 (36.4)	
Preoperative vitamin D				0.054
Normal	396	384 (73.3)	12 (54.5)	
Low	150	140 (26.7)	10 (45.5)	
Preoperative magnesium				0.550
Normal	365	349 (66.6)	16 (72.7)	
Low	181	175 (33.4)	6 (27.3)	
iPTH at 24 hours postoperatively				0.001
Normal	340	334 (63.7)	6 (27.3)	
Low	206	190 (36.3)	16 (72.7)	
Calcium at 24 hours postoperatively				0.009
Normal	343	335 (63.9)	8 (36.4)	
Low	203	189 (36.1)	14 (63.6)	

Data are presented as n (%).

pHPP, permanent hypoparathyroidism; intact parathyroid hormone.

**Table 4.** Multivariate analysis of pHPP at 6 months after total thyroidectomy (n = 546).

Variables	Odds ratio	95% CI	P value
Postoperative calcium			
Normal	1.000		
Low	2.584	1.017–6.567	0.046
Postoperative iPTH			
Normal	1.000		
Low	2.932	1.129–7.616	0.027
Surgical procedure			
Total thyroidectomy	1.000		
Total thyroidectomy plus central dissection	1.674	0.637–4.394	0.296
Age, years			
<45	1.000		
≥45	1.012	0.421–2.430	0.979
Sex			
Male	1.000		
Female	1.420	0.582–3.465	0.442
Preoperative vitamin D			
Normal	1.000		
Low	1.194	0.487–2.925	0.698
Preoperative magnesium			
Normal	1.000		
Low	0.611	0.225–1.658	0.333

pHPP, permanent hypoparathyroidism; intact parathyroid hormone; CI, confidence interval.

showed that the iPTH concentration (OR = 2.932, 95% confidence interval [CI]: 1.129–7.616,  $P = 0.027$ ) and serum calcium concentration (OR = 2.584, 95% CI: 1.017–6.567,  $P = 0.046$ ) 1 day after surgery were independent predictors of the risk of pHPP (Table 4). Lower iPTH and serum calcium concentrations 1 day postoperatively were correlated with a higher likelihood of pHPP.

#### *Use of 1-day postoperative iPTH and serum calcium concentrations to predict occurrence of pHPP at 6 months after surgery*

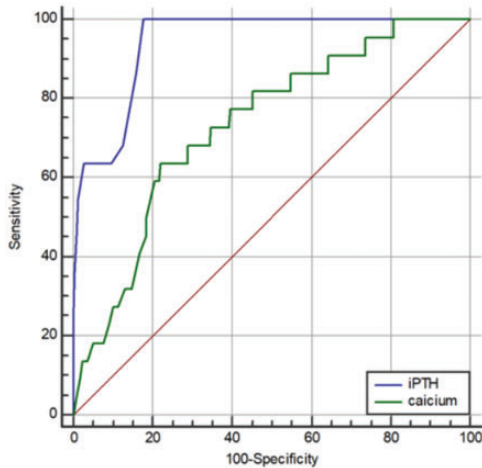
As shown in Figure 1, the receiver operating characteristic curve to predict the occurrence of postoperative pHPP revealed a threshold iPTH concentration of 5.51 pg/mL at 1 day after surgery, with an AUC of 0.956 (95% CI, 0.936–0.972;

$P < 0.001$ ). Its predictive value was high, with a sensitivity of 100%, specificity of 85.1%, PPV of 22%, and NPV of 100%. When the cut-off serum calcium concentration was set at 1.93 mmol/L, the AUC was 0.733 (95% CI, 0.694–0.770;  $P < 0.001$ ). Its predictive value was moderate, with a sensitivity of 63.6%, specificity of 78.1%, PPV of 10.8%, and NPV of 98.1%. In contrast, the predictive value of measuring the iPTH concentration was significantly higher than that of measuring the serum calcium concentration (calculated AUC, 0.956 vs. 0.733; 95% CI, 0.936–0.972 vs. 0.694–0.770;  $P < 0.001$ ).

## **Discussion**

This study showed that pHPP is not a common complication when total thyroidectomy is performed by an experienced surgical team and that a postoperative iPTH





**Figure 1.** Comparison of sensitivity and specificity between serum calcium and intact parathyroid hormone (iPTH) concentrations to predict permanent hypoparathyroidism (pHPP). An iPTH concentration of  $\leq 5.51$  pg/mL at 24 hours after total thyroidectomy had 100% sensitivity and 85.1% specificity to predict pHPP. A postoperative serum calcium concentration  $\leq 1.93$  mmol/L was 63.6% sensitive and 78.1% specific to predict pHPP. The predictive value of iPTH was significantly higher than that of serum calcium.

concentration of  $>5.51$  pg/mL may help to predict which patients will not develop this complication.

Identification and protection of the parathyroid gland is a necessary skill for surgeons who perform thyroid surgery and should not be ignored. Total thyroidectomy still has a risk of hypocalcemia and pHPP, even when performed by the most experienced hands.<sup>14–16</sup> Almquist et al.<sup>17</sup> performed total thyroidectomy in 519 patients with thyroid disease and closely followed them up for a median of 2.7 years (range, 1.2–10.3 years). The multivariate analysis showed that surgical experience, intraoperative accidental parathyroid excision, and the serum PTH and calcium concentrations measured 1 day after total thyroidectomy were independent predictors of the risk of pHPP after thyroid surgery.

In the present study, the incidence of pHPP after total thyroidectomy was 4.03%, which is consistent with the results of other studies.<sup>18–20</sup> Our multifactor analysis showed that the iPTH and serum calcium concentrations measured 1 day postoperatively were closely related to pHPP after thyroid surgery and were independent risk factors.

Several studies showed that a cut-off iPTH value of 15 pg/mL measured 1 day after thyroid surgery could not predict whether the patient would develop pHPP.<sup>21–23</sup> The receiver operating characteristic curve analysis showed that the optimal iPTH threshold was 5.51 pg/mL, which could be expanded to between 5 and 6 pg/mL; this is far lower than the reference data threshold of 15 pg/mL. When an iPTH concentration of 5.51 pg/mL was used as the cut-off point, the AUC was 0.956. In patients with an iPTH concentration of  $\leq 5.51$  pg/mL measured at 24 hours after surgery, the sensitivity was 100% for a high risk of pHPP, with a PPV of 22%. The reason for this may be that the final incidence of pHPP was only 4.03%, with a higher predicted false-positive rate. After the operation, the parathyroid function remains in a state of dynamic recovery. Over time, the potentially impaired parathyroid gland function is likely to recover, and it is difficult to predict whether pHPP will develop. An iPTH concentration of  $\leq 5.51$  pg/mL indicates to some extent that the iPTH concentration is not likely to return to the reference range within a short period of time and that there is a high risk of pHPP. However, in patients with an iPTH concentration of  $>5.51$  pg/mL, the specificity was 85.1% and NPV was 100%; this was predictive of normal parathyroid function 6 months after surgery. Almost all patients who were excluded would have a risk of pHPP. The reason may be that a higher iPTH concentration on day 1 postoperatively is associated with less damage to the parathyroid

during the operation, a better the blood supply to the parathyroid gland, and more rapid return of parathyroid function to the normal level after surgery. Julián et al.<sup>24</sup> conducted a prospective study of 70 patients with thyroid surgery and came to a similar conclusion. At 24 hours after surgery, when the iPTH concentration was  $\leq 5.8$  pg/mL, the PPV of pHPP was 30% and NPV was 100%. Hermann et al.<sup>25</sup> found that the determination of PTH after total thyroidectomy was more advantageous in estimating the occurrence of hypocalcemia than the determination of the serum calcium concentration. The PTH concentration largely determined the occurrence of hypocalcemia. Compared with determination of the iPTH concentration in the present cohort, when the postoperative serum calcium concentration was  $\leq 1.93$  mmol/L, the sensitivity was 63.6%, the specificity was 78.1%, and the PPV was only 10.8%. The predictive value of the iPTH concentration was significantly higher than that of the serum calcium concentration. The AUC of  $>0.9$  for the iPTH level measured 1 day after total thyroidectomy suggests the excellent accuracy of this diagnostic test for assessing the occurrence of pHPP after the operation. The serum calcium concentration 1 day postoperatively had a lower accuracy of predicting the occurrence of pHPP.

In thyroid surgery, whether the serum iPTH concentration should be conducted intraoperatively, several hours postoperatively, or 1 day postoperatively is controversial.<sup>26-28</sup> In published studies, the timing of iPTH measurements has ranged from 10 minutes to 24 hours after surgery. McLeod et al.<sup>29</sup> found that a PTH concentration of  $<12$  pg/mL measured 20 minutes after the operation could predict the occurrence of hypocalcemia, with a sensitivity of 100% and a specificity of 92%. Sywak et al.<sup>30</sup> reported that a low PTH concentration of 3 to 10 pg/mL measured 4 hours

after surgery had a sensitivity of 90% and a specificity of 84% for predicting postoperative hypocalcemia. Asari et al.<sup>31</sup> reported that an iPTH concentration of  $\leq 15$  pg/mL at 1 day after surgery predicted hypoparathyroidism with a sensitivity of 97.7% and a specificity of 82.6%. In this study, we determined an iPTH threshold of  $\leq 5.51$  pg/mL at 1 day after total thyroidectomy for predicting postoperative pHPP with a sensitivity of 100% and a specificity of 85.1%. Therefore, the best time to measure the serum iPTH concentration is 1 day after surgery to predict whether pHPP will occur after thyroidectomy; this strategy has good feasibility and effectiveness. However, our observation in the present study was limited by a certain deviation in the postoperative time interval (16% loss of information; e.g., some patients might have been tested 20 hours postoperatively and other sooner than that) and by great variability in the time to iPTH measurement.

The present study has some limitations. The study was a retrospective analysis and lacked randomization control. This highlights the risk factors for predicting postoperative pHPP in thyroid surgery and demonstrates the need for more prospective studies in this field. Several parameters have been associated with the risk of pHPP, including the postoperative PTH concentration, decline in PTH concentration between the preoperative and postoperative measurements, degree of decrease in the magnesium concentration, T stage, and whether parathyroid autotransplantation was carried out.<sup>32-35</sup> Our results may be biased because the risk of unwanted parathyroid removal is higher when the resection is larger. The percentage of parathyroid glands removed at surgery and/or autotransplanted was likewise not analyzed. Further studies are required to include these relevant factors, all of which may help to assess the risk of developing pHPP postoperatively.

## Conclusions

The iPTH concentration measured 1 day after total thyroidectomy is closely related to the occurrence of pHPP postoperatively and is an independent predictive risk factor. Postoperative measurement of the iPTH concentration can be helpful in identifying patients at risk for developing pHPP. The predictive value of the iPTH concentration measured after surgery is much higher than that of the serum calcium concentration. If the concentration of iPTH is  $>5.51$  pg/mL, patients are less likely to develop pHPP after surgery. In contrast, if the measured iPTH concentration is  $\leq 5.51$  pg/mL, there is a higher risk of pHPP postoperatively.

## Abbreviations

iPTH = intact parathyroid hormone, PTH = parathyroid hormone, pHPP = permanent hypoparathyroidism, AUC = area under the curve, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value.

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## Author contributions

Conceptualization: Cai SY, Gao ZG  
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All authors read and approved the final manuscript.

## Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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