

Predictive Factors for Diagnosis of Parathyroid Carcinoma in Primary Hyperparathyroidism

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ABSTRACT

Background: Parathyroid carcinoma (PC) is a rare endocrine cancer. Preoperative diagnosis is challenging because some of its clinical and biochemical features overlap with those of benign parathyroid disease; however, preoperative identification is important for appropriate surgical planning, as en bloc resection at the initial operation can improve patient outcomes.

Objective: To identify preoperative factors associated with PC in patients with primary hyperparathyroidism and to evaluate their predictive capacity.

Materials and Methods: A retrospective case-control study was conducted of patients with primary hyperparathyroidism who had undergone parathyroidectomy at Rajavithi Hospital between January 2008 and December 2023. Patients were divided into PC and benign groups based on pathological reports. Demographic, clinical, laboratory, and imaging data of the groups were compared. Binary logistic regression was used to identify the factors that predicted PC, and ROC curve analysis was performed to determine optimal cutoff values.

Results: Of 102 patients, 12 (11.8%) had PC and 90 had benign disease. After multivariate analysis, palpable neck mass (adjusted OR 11.31, 95% CI 2.17 to 59.09, $p=0.004$) and serum calcium ≥ 13.35 mg/dL (adjusted OR 12.02, 95% CI 1.32 to 109.27, $p=0.027$) were independent predictors of PC. Serum calcium demonstrated good diagnostic performance (AUC 0.834), with a high negative predictive value (98.4%).

Conclusion: A palpable neck mass and severe hypercalcemia are the key predictors of PC in primary hyperparathyroidism. These two simple factors can assist clinicians in PC diagnosis and surgical planning.

Keywords: Parathyroid cancer; Parathyroid carcinoma; Primary hyperparathyroidism; Benign parathyroid tumor; Parathyroid adenoma; Parathyroid hyperplasia; Hypercalcemia

Received 30 March 2026 | Revised 19 May 2026 | Accepted 20 May 2026

J Med Assoc Thai 2026;109(9):758-63

<https://doi.org/10.35755/jmedassocthai.2026.9.04520>

Parathyroid carcinoma (PC) is a rare endocrine cancer, accounting for approximately 0.005% of all cancers⁽¹⁾ and is present in 0.5-5% of patients with primary hyperparathyroidism^(2,3). It affects males and females equally and is most commonly diagnosed in those aged 50 years and older⁽⁴⁻⁶⁾. Patients with PC exhibit elevated parathyroid hormone levels, resulting in symptoms related to hypercalcemia such as nausea, vomiting, constipation, fatigue, mood changes, weight loss, bone pain, osteoporosis, muscle pain, and kidney stones.

The clinical presentations and laboratory findings of PC are indistinguishable from those of primary hyperparathyroidism caused by other non-malignant conditions, such as parathyroid adenoma or hyperplasia. This makes preoperative diagnosis challenging, and it is usually confirmed only by histopathological examination after surgery⁽⁷⁾. Consequently, this affects surgical planning, as patients with PC require more extensive surgical resection^(3,8-10), which carries a higher risk of injury to adjacent tissues compared to surgery performed for benign parathyroid disease.

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How to cite this article:

Tanamai N. Predictive Factors for Diagnosis of Parathyroid Carcinoma in Primary Hyperparathyroidism. J Med Assoc Thai 2026;109:758-63.

What is already known about this topic?

PC is a rare endocrine malignancy, and its characteristics overlap with those of benign parathyroid diseases. Previous studies have reported that a palpable neck mass, markedly elevated parathyroid hormone levels, severe hypercalcemia, and large tumor size on ultrasound are preoperative factors associated with PC.

What does this study add?

Palpable neck mass (adjusted OR 11.31) and serum calcium cut-off ≥ 13.35 mg/dL (adjusted OR 12.02) are the two strongest independent predictive factors of PC in patients with primary hyperparathyroidism. This calcium cutoff also demonstrates a good diagnostic accuracy (AUC 0.834) and a high negative predictive value (98.4%).

Although several studies have identified clinical features associated with PC^(7,11-13), evidence on the most practical preoperative predictors remains limited, and no optimal cut-off points have been established, particularly for distinguishing PC from benign parathyroid disease in the Thai population. Therefore, this study aims to evaluate preoperative factors that are associated with the occurrence of PC in patients presenting with primary hyperparathyroidism and to assess the predictive capacity of these factors in forecasting PC.

MATERIALS AND METHODS

A retrospective case-control study was conducted of patients diagnosed with primary hyperparathyroidism who underwent parathyroidectomy at the Center of Excellence in Otolaryngology Head and Neck Surgery, Rajavithi Hospital. Patients were included if they had pathological confirmation of either benign parathyroid neoplasms (adenoma or hyperplasia), which were defined as the control group, or PC, defined as the case group, between January 2008 and December 2023. A case-control ratio of 1:10 was applied, and the sample size was determined based on the available data from the hospital database during the study period. As this was a retrospective study, the potential for bias was considered, and selection bias was minimized by applying predefined inclusion criteria, while information bias was reduced through standardized data collection from the medical records.

Baseline demographic and clinical data were collected from the hospital medical record system, including sex, age, comorbidities, presenting symptoms, and clinical manifestations such as neck mass and vocal cord mobility. Laboratory parameters included preoperative intact parathyroid hormone (iPTH), serum calcium, phosphate, and alkaline phosphatase (ALP) levels. Radiological data consisted of technetium-99m sestamibi (MIBI) scan and neck ultrasonography. Missing data in some patients' records were handled by using complete-case analysis, and no imputation was performed because the proportion of missing data was small and unlikely to affect the results. The patients provided informed consent for the use of their medical records. The study protocol was approved by the the Ethics Committee of Rajavithi Hospital (No. 155/2567) and was registered with the Thai Clinical Trials Registry, TCTR20260321005.

Statistical analyses were done with IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA), and descriptive statistics were used to summarize baseline characteristics. Categorical variables were

presented as frequencies and percentages, while continuous variables were presented as mean $\pm$ standard deviation (SD) for normally distributed data, and as median with minimum and maximum values for non-normally distributed data. Comparisons between categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables in two independent groups were compared using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Factors associated with PC were analyzed using binary logistic regression, and the results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values for diagnostic purposes, with results presented as the area under the curve (AUC). A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 102 patients with primary hyperparathyroidism who had undergone parathyroid surgery with histopathological confirmation were included in this study. Of these, 12 (11.8%) were diagnosed with PC (case group), while 90 were found to have benign parathyroid disease, parathyroid adenoma, or parathyroid hyperplasia (control group).

Demographic, Biochemical, and Imaging Characteristics

Baseline demographic and clinical characteristics of both groups are shown in [Table 1](#). There were no statistically significant differences between the case and control groups in terms of sex distribution, age at diagnosis, presence of comorbidities (such as diabetes mellitus, hypertension, gout, or chronic kidney disease), or symptoms related to hypercalcemia, such as constipation, bone pain, pathological fractures, renal or ureteric stones, and fatigue. A palpable neck mass was significantly more frequent in patients with PC than in those with benign disease (60.0% vs. 10.0%, $p=0.001$). Vocal cord paralysis was observed in only one patient in the carcinoma group, with no statistically significant difference between the groups.

Patients with PC had significantly higher serum iPTH levels than those in the benign group (median 1,480.00 pg/mL [range 469.00-2,913.00] vs. 528.50 pg/mL [range 10.30-2,920.00], $p=0.024$). Mean serum calcium levels were also significantly higher in PC patients than in their counterparts in the benign group (15.99 ± 3.13 mg/dL vs. 12.80 ± 1.49 mg/dL, $p=0.016$). In addition, serum ALP levels were significantly

Table 1. Comparison of demographic, biochemical characteristics, and imaging findings in parathyroid carcinoma and benign parathyroid disease

Parameters	CA parathyroid (n=12)	Benign parathyroid (n=90)	p-value
Sex; n (%)			0.107
Male	7 (58.3)	29 (32.2)	
Female	5 (41.7)	61 (67.8)	
Age at diagnosis (years); mean±SD	49.42±14.83	57.30±13.93	0.070
Underlying diseases; n (%)			0.718
Yes	9 (75.0)	71 (78.9)	
No	3 (25.0)	19 (21.1)	
Symptoms related to hyperparathyroidism; n (%)			0.529
Present	9 (75.0)	56 (62.2)	
Not present	3 (25.0)	34 (37.8)	
Neck mass; n (%)			0.001*
Present	6 (60.0)	9 (10.0)	
Not present	4 (40.0)	81 (90.0)	
Vocal cord mobility; n (%)			0.118
Normal movement	11 (91.7)	90 (100)	
Paralysis	1 (8.3)	0 (0.0)	
Serum iPTH, median (pg/mL); median (min-max)	1480.00 (469.00-2913.00)	528.50 (10.30-2920.00)	0.024* ^M
Serum calcium (mg/dL); mean±SD	15.99±3.13	12.80±1.49	0.016* ^T
Serum phosphate (mg/dL); mean±SD	2.58±0.89	2.23±0.45	0.278
ALP (IU/L); median (min-max)	680.00 (206.00-1008.00)	133.00 (41.00-1899.00)	0.004* ^M
MIBI; n (%)			1.000
Positive	7 (87.5)	79 (88.8)	
Negative	1 (12.5)	10 (11.2)	
Neck US for tumor size; mean±SD	3.24±1.80	2.01±1.24	0.042* ^T

SD=standard deviation; iPTH=intact parathyroid hormone; ALP=alkaline phosphatase; MIBI=technetium-99m sestamibi scan; US=ultrasound

* Statistically significant at p<0.05, (M) Mann-Whitney U test, (T) Independent t-test

Table 2. Univariate and multivariate analyses of factors associated with parathyroid carcinoma

Parameters	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Neck mass	13.50 (3.20 to 57.00)	<0.001*	11.31 (2.17 to 59.09)	0.004*
Calcium (≥13.35 mg/dL)	18.67 (2.23 to 156.64)	0.007*	12.02 (1.32 to 109.27)	0.027*

OR=odds ratio; CI=confidence interval

* Statistically significant at p<0.05

elevated in patients with PC (median 680.00 IU/L [range 206.00-1,008.00] vs. 133.00 IU/L [range 41.00-1,899.00], p=0.004). There were no significant differences between the groups in terms of serum phosphorus levels or MIBI scan positivity (p=0.278 and 1.000, respectively). Tumor size measured by neck ultrasonography was significantly larger in the carcinoma group (3.24±1.80 cm vs. 2.01±1.24 cm, p=0.042).

Factors Associated with Parathyroid Carcinoma

Binary logistic regression analysis was performed to identify factors associated with PC (Table 2). In

univariate analysis, palpable neck mass and elevated serum calcium levels were significantly associated with PC. After adjustment for potential confounders, both factors remained independent predictors. A palpable neck mass was associated with an adjusted OR of 11.31 (95% CI 2.17 to 59.09; p=0.004), while serum calcium ≥13.35 mg/dL was associated with an adjusted OR of 12.02 (95% CI 1.32 to 109.27, p=0.027). Collinearity testing demonstrated an association between neck mass and tumor size on ultrasonography, as well as between serum calcium and iPTH and ALP levels; therefore, only the most clinically relevant variables were included in the study.

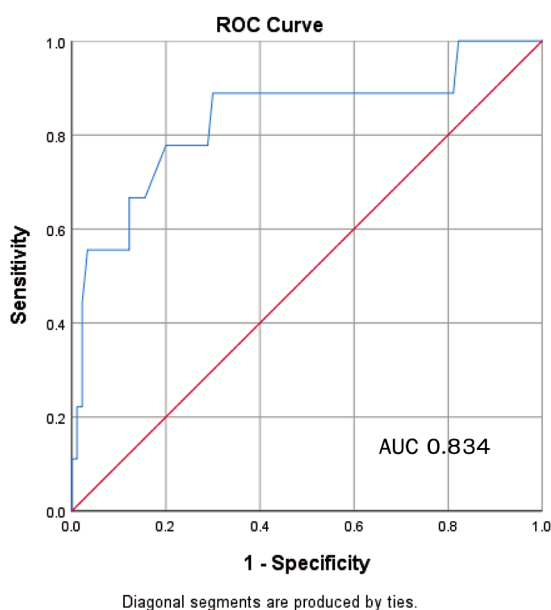


Figure 1. ROC curve of serum calcium for predicting parathyroid carcinoma. The area under the curve was 0.834 ($p=0.001$).

Diagnostic Performance of Serum Calcium

The optimal cut-off value of serum calcium for predicting PC was determined by ROC curve analysis (Figure 1). The AUC was 0.834 ($p=0.001$), indicating good diagnostic accuracy. A serum calcium cut-off value of 13.35 mg/dL yielded a sensitivity of 88.9%, specificity of 70.0%, positive predictive value of 22.9%, negative predictive value of 98.4%, and overall diagnostic accuracy of 71.7%.

DISCUSSION

PC is a rare endocrine malignancy and accounts for 0.5% to 5% of cases of primary hyperparathyroidism^(2,3,7,14). The prevalence of PC in this study was relatively high (11.8%) among patients with primary hyperparathyroidism, but it was comparable with reports from other Asian countries, including Korea (4.7% and 5.7%)^(7,11), China (8.1%)⁽¹³⁾, Japan (5%)⁽¹⁵⁾, India (3.7%)⁽¹⁶⁾, and another institute in Thailand (9%)⁽¹⁷⁾. This finding may be attributable to the tertiary care setting to which complicated hypercalcemia cases suspected of PC are preferentially referred; furthermore, asymptomatic hypercalcemia may be underdiagnosed or managed conservatively by endocrinologists.

No significant differences between genders or ages were observed in this study. The gender distribution among patients with PC was equal, whereas benign parathyroid tumors were more commonly observed

in women, consistent with other findings in the literature^(7,12,18). The mean age at diagnosis of PC was 49.42 years, which was comparable to that reported in other studies, ranging from 45 to 55 years^(13,18,19).

Preoperative differentiation between PC and benign parathyroid disease remains challenging, as PC has clinical and biochemical features that overlap with those of hypercalcemia^(7,11,13,20). Accurate preoperative identification is essential in order to allow complete en bloc resection at the initial surgery, offering the best chance for disease control and long-term survival^(8,10). In the present study, we identified two independent predictive factors for PC: palpable neck mass and markedly elevated serum calcium levels.

A palpable neck mass is strongly associated with PC, with an adjusted OR of 11.3. This may be explained by aggressive growth or PC local invasion, resulting in a clinically detectable cervical mass, and this is consistent with the findings of previous reports. Kawai et al.⁽¹¹⁾ proposed that a palpable neck mass is one of the factors suggestive of PC, along with elevated serum calcium levels and irregular margins on ultrasonography. Selvan et al.⁽¹⁶⁾ identified a palpable neck mass as one of three suspicious features of PC, together with high serum calcium levels and intraoperative substrap adhesions. Similarly, Nam et al.⁽²¹⁾ reported that palpability of the neck mass in PC was the only factor that was significantly different from cases of parathyroid adenoma (unlike age, iPTH, and serum calcium), although PC also appeared significantly larger on ultrasonography. In contrast, benign parathyroid adenomas are usually small, soft, and rarely palpable on physical examination.

Severe hypercalcemia is another hallmark of PC due to excessive hormone-driven bone resorption, renal reabsorption and intestinal absorption. In our study, a serum calcium level cut-off of ≥ 13.35 mg/dL is independently associated with PC (adjusted OR 12.02). Consistent with our findings, previous studies have reported significantly higher serum calcium levels in PC than in benign disease⁽²⁰⁾. Kawai et al.⁽¹¹⁾ and Selvan et al.⁽¹⁶⁾ reported serum calcium levels of greater than 14 mg/dL, suggestive of PC, while Xue et al.⁽¹³⁾ proposed a lower cutoff value of 12.5 mg/dL for predicting PC.

Elevated serum iPTH and alkaline phosphatase levels are also significantly higher in patients with PC, reflecting increased tumor burden and accelerated bone turnover secondary to sustained parathyroid hormone excess. Several previous studies^(12,13) have also reported significantly higher serum iPTH and ALP levels in PC compared with benign parathyroid

tumors. However, due to collinearity among serum iPTH, calcium, and ALP, serum calcium was selected as the clinically relevant biochemical marker in the multivariate model. Similarly, tumor size measured by ultrasonography was larger in the carcinoma group but showed collinearity with the presence of a neck mass, limiting its independent predictive value.

ROC curve analysis demonstrated that serum calcium had good discriminative ability for predicting PC, with an AUC of 0.834. Although the positive predictive value is low, the high negative predictive value suggests that serum calcium is particularly useful for excluding malignancy in patients with primary hyperparathyroidism.

The results of this study highlight the importance of integrating simple clinical examination and routine biochemical parameters into preoperative risk stratification. Patients presenting with a palpable neck mass and severe hypercalcemia should be considered at high risk for PC and may benefit from referral to experienced surgeons and planning for en bloc resection at the initial operation.

This study has several limitations: it was performed in a single center, had a retrospective design, and involved a small number of carcinoma cases; this may have introduced information bias due to inaccuracies in the medical records. Selection bias may also have occurred, as the study was conducted in a tertiary center, where more complex cases were likely to be referred, which may limit the generalizability of the findings. Nevertheless, given the rarity of PC, our findings provide practical information and support the existing literature regarding predictive factors for malignancy.

CONCLUSION

In patients with primary hyperparathyroidism, a palpable neck mass and severe hypercalcemia are key predictors of PC and may assist clinicians in preoperative risk assessment and in planning appropriate surgical management.

Acknowledgement

The author would like to thank Dr. Pornake Apipan and Dr. Somjin Chindavichak for their advice and support, Mr. John Flanagan for editing the manuscript. The author would also like to express her deep appreciation for the assistance of Miss Sirinat Treesinchai and the staff of the Department of Research and Technology Assessment in reviewing the proposal and providing guidance on statistical analysis.

Authors Contributions

The author (NT) designed the study, collected data, and wrote the manuscript.

Clinical Trial Registration

This study was registered with the Thai Clinical Trials Registry, and its identification number was TCTR20260321005.

Conflicts of Interest

The author has no conflicts of interest to declare.

Data Availability Statement

The data of this study are available from the corresponding author upon reasonable request with ethics approval.

Ethics Approval and Consent to Participate

This study protocol was approved by the Ethics Committee of Rajavithi Hospital (No. 155/2567).

Funding Disclosure

This study was funded by Rajavithi Hospital. The funding source had no role in the study design, data collection, analysis, or manuscript preparation.

Use of Artificial Intelligence

The author used Perplexity version 2.260206.0 to assist with language refining, and the manuscript was reviewed and approved by the author.

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