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Development Of A Multidisciplinary Risk Prediction Model For Hypocalcemia Following Total Thyroidectomy: A Prospective Observational Study.

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Abstract

Background: Postoperative hypocalcemia is one of the most frequent complications following total thyroidectomy and may result from transient or permanent impairment of parathyroid function. Its occurrence is influenced by multiple patient-related, biochemical, and surgical factors. Although postoperative parathyroid hormone (PTH) is widely used for early risk assessment, reliance on a single biochemical parameter may not adequately account for the multifactorial nature of postoperative hypocalcemia. A multidisciplinary prediction model incorporating clinical, biochemical, and operative variables may therefore improve individualized risk stratification. ***Aim:*** To develop a multidisciplinary risk-prediction model for early identification of hypocalcemia following total thyroidectomy. ***Materials and Methods:*** This prospective observational study included 200 adult patients undergoing total thyroidectomy at a tertiary care teaching hospital. Demographic and clinical characteristics, preoperative calcium, PTH, vitamin D, magnesium, thyroid pathology, and relevant perioperative variables were recorded. Surgical variables including neck dissection, number of parathyroid glands identified and preserved, parathyroid autotransplantation, inadvertent parathyroidectomy, and duration of surgery were documented. Postoperative PTH, percentage decline in PTH, corrected serum calcium, and magnesium were assessed. Patients were categorized into hypocalcemia and normocalcemia groups. ***Results:*** Among 200 patients, 62 (31.0%) developed postoperative hypocalcemia, while 138 (69.0%) remained normocalcemic. Female sex (83.9% vs 65.9%; p=0.009), malignant thyroid disease (40.3% vs 25.4%; p=0.033), thyroiditis (27.4% vs 13.8%; p=0.019), vitamin D deficiency (56.5% vs 32.6%; p=0.001), and hypomagnesemia (25.8% vs 9.4%; p=0.002) were significantly associated with hypocalcemia. Mean preoperative calcium was significantly lower among hypocalcemic patients (9.02 ± 0.41 vs 9.31 ± 0.39 mg/dL; p<0.001). Central neck dissection (38.7% vs 19.6%; p=0.004), inadvertent parathyroidectomy (16.1% vs 3.6%; p=0.003), parathyroid autotransplantation (22.6% vs 9.4%; p=0.011), and operative duration >150 minutes (46.8% vs 28.3%; p=0.010) were significantly associated with hypocalcemia. Early postoperative PTH was significantly lower in the hypocalcemia group (10.8 ± 6.4 vs 28.6 ± 12.7 pg/mL; p<0.001). On multivariable analysis, female sex (aOR 2.18), vitamin D <20 ng/mL (aOR 2.42), preoperative calcium <9.0 mg/dL (aOR 2.37), central neck dissection (aOR 2.51), inadvertent parathyroidectomy (aOR 3.46), PTH decline >60% (aOR 3.71), and postoperative PTH <15 pg/mL (aOR 5.84) were independent predictors. The multidisciplinary model demonstrated an AUC of 0.89 (95% CI 0.84–0.94) with 83.9% sensitivity, 84.8% specificity, 71.2% positive predictive value, and 92.1% negative predictive value. ***Conclusion:*** Postoperative hypocalcemia occurred in nearly one-third of patients following total thyroidectomy and was independently associated with a combination of clinical, biochemical, and surgical factors. Postoperative PTH <15 pg/mL was the strongest individual predictor; however, the multidisciplinary risk-prediction model demonstrated superior overall predictive performance. Integration of preoperative calcium and vitamin D status, postoperative PTH dynamics, and operative factors may facilitate early identification of high-risk patients and support individualized postoperative monitoring and supplementation strategies. Further internal and external validation is required before clinical implementation of the model.

Keywords: Total thyroidectomy; postoperative hypocalcemia; parathyroid hormone; vitamin D; parathyroidectomy.

INTRODUCTION

Total thyroidectomy is a widely performed surgical procedure for the management of malignant thyroid disease, multinodular goitre, Graves' disease, and selected benign thyroid disorders. Although improvements in surgical technique and perioperative care have considerably reduced procedure-related morbidity, postoperative hypocalcemia remains one of the most frequent complications following total thyroidectomy and represents an important cause of patient discomfort, prolonged hospitalization, additional biochemical monitoring, treatment, and readmission. The principal mechanism is transient or permanent impairment of parathyroid function resulting from inadvertent removal, devascularization, direct trauma, or disruption of the blood supply of the parathyroid glands during thyroid dissection.

The American Thyroid Association has emphasized that postoperative hypoparathyroidism is the most common complication following bilateral thyroid surgery and that early identification of patients at risk is important for appropriate postoperative management.[1] The clinical manifestations of postoperative hypocalcemia range from asymptomatic biochemical abnormalities to perioral numbness, paresthesia, muscle cramps, carpopedal spasm, tetany, seizures, laryngospasm, and potentially life-threatening cardiac arrhythmias.

The reported frequency varies substantially according to patient population, extent of surgery, definition of hypocalcemia, timing of calcium assessment, surgeon experience, and underlying thyroid pathology. A systematic review and meta-analysis by Edafe et al. demonstrated that biochemical hypocalcemia occurs commonly after thyroid surgery and identified several patient-, disease-, biochemical-, and surgery-related predictors.[2] Another meta-analysis involving 23 studies identified hypoparathyroidism (OR 5.58), total thyroidectomy (OR 3.59), hypomagnesemia (OR 2.85), vitamin D deficiency (OR 2.32), female sex (OR 1.49), thyroid malignancy (OR 1.85), thyroiditis (OR 1.48), and neck dissection among significant predictors of postoperative hypocalcemia.[3] Thus, the development of hypocalcemia is multifactorial rather than attributable to a single surgical factor. The postoperative parathyroid hormone (PTH) concentration has emerged as one of the most useful early biochemical predictors because of the short biological half-life of PTH and its rapid decline following parathyroid injury. Grodski and Serpell demonstrated that perioperative PTH measurement could facilitate early prediction of post-thyroidectomy hypocalcemia and guide calcium supplementation and discharge planning.[4]

Similarly, prospective evidence has demonstrated that a 56% decline in PTH on the first postoperative day predicted hypocalcemia with approximately 80% sensitivity and specificity.[5] Preoperative vitamin D status may further modify the relationship between postoperative PTH and calcium homeostasis, emphasizing the importance of integrating biochemical rather than isolated PTH measurements into prediction strategies. In the Indian context, vitamin D deficiency is common and may represent an additional clinically relevant contributor to postoperative calcium disturbances. A prospective Indian study by Pradeep and Ramalingam involving 203 total thyroidectomy patients demonstrated that vitamin D status influenced the predictive performance of postoperative PTH for hypocalcemia, highlighting the importance of considering both variables in Indian patients.[6]

More recent Indian evidence from Thakur et al. also demonstrated the utility of postoperative serum PTH for predicting hypocalcemia following total thyroidectomy.[7] Despite the availability of individual predictors, postoperative decision-making is frequently based on isolated laboratory values or clinical judgement rather than a structured combination of patient-, biochemical-, surgical-, and anesthetic factors. A multidisciplinary risk-prediction model incorporating demographic characteristics, thyroid pathology, preoperative calcium, vitamin D and magnesium levels, perioperative PTH changes, surgical complexity, parathyroid gland preservation, neck dissection, duration of surgery, and relevant perioperative factors could provide more individualized risk estimation. Such a model could identify low-risk patients suitable for early discharge while allowing high-risk patients to receive intensified biochemical monitoring and early calcium and vitamin D supplementation. Therefore, the present study was undertaken to develop a multidisciplinary risk-prediction model for hypocalcemia following total thyroidectomy, integrating clinical, biochemical, surgical, and perioperative variables to facilitate early identification and appropriate management of high-risk patients.

AIM

To develop a multidisciplinary risk-prediction model for early identification of hypocalcemia following total thyroidectomy.

OBJECTIVES

Primary Objective

1. To identify the clinical, biochemical, surgical, and perioperative predictors associated with the development of hypocalcemia following total thyroidectomy.

Secondary Objectives

2. To develop and internally evaluate a multivariable risk-prediction model for postoperative hypocalcemia using significant independent predictors.
3. To assess the predictive performance of postoperative PTH, serum calcium, vitamin D, magnesium, and relevant surgical factors for early identification of patients at risk of postoperative hypocalcemia..

MATERIALS AND METHODS

Study Design

The study was conducted as a prospective observational study for the development of a clinical risk-prediction model.

Study Population

Adult patients undergoing elective total thyroidectomy for benign or malignant thyroid diseases during the study period were prospectively recruited.

SAMPLE SIZE

A total of 200 patients undergoing total thyroidectomy were included in the study.
The sample size was selected considering an anticipated postoperative hypocalcemia frequency of approximately 30% based on previous published studies and the requirement for an adequate number of outcome events for development of a multivariable prediction model.

With 200 patients and an anticipated hypocalcemia rate of approximately 30%, approximately 60 hypocalcemia events were expected, providing sufficient events for a parsimonious multivariable model containing approximately 5–6 key independent predictors while reducing the risk of model overfitting.
Hence, the final sample size was taken as:
N = 200 patients.

Sampling Technique

A consecutive sampling technique was used. All eligible patients undergoing total thyroidectomy during the study period were consecutively recruited until the required sample size of 200 was achieved.

INCLUSION CRITERIA

1. Patients aged 18 years and above were included.
2. Patients undergoing elective total thyroidectomy for benign or malignant thyroid disease were included.
3. Patients who provided written informed consent were included.

EXCLUSION CRITERIA

1. Patients with pre-existing hypocalcemia were excluded.
2. Patients with known hypoparathyroidism or parathyroid disorders were excluded.
3. Patients with severe chronic kidney disease affecting calcium metabolism were excluded.
4. Patients receiving medications known to substantially interfere with calcium metabolism, where clinically relevant, were excluded.
5. Patients with incomplete perioperative biochemical or clinical data were excluded.
6. Patients who refused consent were excluded.

STUDY PROCEDURE

After enrolment, demographic and clinical characteristics including age, sex, body mass index, presenting diagnosis, duration of thyroid disease, comorbidities, previous thyroid surgery, symptoms of hyperthyroidism, and relevant medication history were recorded. Preoperative biochemical investigations included serum total calcium, albumin, corrected calcium, intact parathyroid hormone, 25-hydroxyvitamin D, magnesium, phosphate, thyroid function tests, renal function tests, and other routine preoperative investigations. Vitamin D deficiency and other biochemical abnormalities were documented according to predefined laboratory reference ranges.

Surgical Assessment

Operative variables including indication for thyroidectomy, thyroid gland size, benign or malignant pathology, presence of thyroiditis, retrosternal extension, duration of surgery, central or lateral neck dissection, number of parathyroid glands identified and preserved, inadvertent parathyroidectomy, parathyroid autotransplantation, and surgeon-related operative details were prospectively documented.

Anesthetic and Perioperative Assessment

Relevant anesthetic variables including duration of anesthesia, intraoperative fluid administration, blood loss, blood transfusion, hemodynamic instability, and other significant perioperative events were recorded.

POSTOPERATIVE ASSESSMENT

Serum calcium and relevant biochemical parameters were measured postoperatively according to the institutional protocol. Postoperative intact PTH was measured within the predefined early postoperative period, and the percentage decline from the preoperative PTH concentration was calculated.

Patients were clinically assessed for manifestations of hypocalcemia, including perioral numbness, paresthesia, muscle cramps, carpopedal spasm, Chvostek sign, Trousseau sign, tetany, seizures, and cardiac manifestations.
The requirement for oral or intravenous calcium supplementation and calcitriol therapy was documented.

OUTCOME DEFINITION

The primary outcome was the development of postoperative hypocalcemia following total thyroidectomy, defined using the institutional laboratory lower reference limit for albumin-corrected serum calcium and/or clinically significant hypocalcemic symptoms requiring treatment.

Patients were categorized into:
Hypocalcemia group: Patients who developed biochemical and/or clinically significant postoperative hypocalcemia.
Normocalcemia group: Patients who maintained normal postoperative calcium concentrations without clinically significant hypocalcemia.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation or median with interquartile range depending on data distribution. Categorical variables were expressed as frequencies and percentages. The independent Student's t-test or Mann–Whitney U test was used to compare continuous variables between patients with and without postoperative hypocalcemia. The Chi-square test or Fisher's exact test was used for categorical variables.

Potential predictors were initially assessed using univariate analysis. Clinically relevant variables and variables demonstrating appropriate statistical association were subsequently evaluated using multivariable binary logistic regression.

Independent predictors were expressed as adjusted odds ratios (aOR) with 95% confidence intervals. A prediction model was developed using the final independent predictors. Model discrimination was evaluated using the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC). An optimal probability cut-off was identified, and the sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Model calibration was assessed by comparing predicted and observed probabilities of postoperative hypocalcemia. Internal validation was performed using bootstrap resampling to estimate optimism-corrected model performance and reduce the likelihood of overfitting. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1. Baseline clinical and biochemical characteristics according to postoperative hypocalcemia status (N=200)

Variable	Hypocalcemia (n=62)	Normocalcemia (n=138)	p-value
Age, years	45.8 ± 12.6	47.2 ± 13.1	0.482
Female sex	52 (83.9%)	91 (65.9%)	**0.009**
BMI, kg/m²	25.1 ± 3.8	24.6 ± 3.6	0.374
Malignant thyroid disease	25 (40.3%)	35 (25.4%)	**0.033**
Thyroiditis	17 (27.4%)	19 (13.8%)	**0.019**
Preoperative calcium, mg/dL	9.02 ± 0.41	9.31 ± 0.39	**<0.001**
Preoperative PTH, pg/mL	42.8 ± 15.6	45.3 ± 16.1	0.306
Vitamin D <20 ng/mL	35 (56.5%)	45 (32.6%)	**0.001**
Magnesium <1.7 mg/dL	16 (25.8%)	13 (9.4%)	**0.002**

Interpretation: Postoperative hypocalcemia developed in **62 of 200 patients (31.0%)**. Female sex, malignant thyroid disease, thyroiditis, lower preoperative serum calcium, vitamin D deficiency, and hypomagnesemia were significantly associated with postoperative hypocalcemia. Age, BMI, and baseline PTH did not differ significantly between groups. These findings suggest that several clinically identifiable preoperative factors may contribute to hypocalcemia risk.

Table 2. Association of operative factors with postoperative hypocalcemia

Operative factor	Hypocalcemia (n=62)	Normocalcemia (n=138)	p-value
Central neck dissection	24 (38.7%)	27 (19.6%)	**0.004**
Lateral neck dissection	11 (17.7%)	10 (7.2%)	**0.024**
≥3 parathyroid glands identified/preserved	35 (56.5%)	106 (76.8%)	**0.003**
Parathyroid autotransplantation	14 (22.6%)	13 (9.4%)	**0.011**
Inadvertent parathyroidectomy	10 (16.1%)	5 (3.6%)	**0.003**
Operative duration >150 min	29 (46.8%)	39 (28.3%)	**0.010**
Estimated blood loss >200 mL	13 (21.0%)	16 (11.6%)	0.081

Interpretation: Central and lateral neck dissection were significantly associated with postoperative hypocalcemia. Patients in whom ≥3 parathyroid glands were identified and preserved had a lower frequency of hypocalcemia, whereas parathyroid autotransplantation and inadvertent parathyroidectomy were significantly more common among patients who developed hypocalcemia. Longer operative duration was also significantly associated with hypocalcemia, suggesting that surgical complexity and parathyroid manipulation contributed substantially to postoperative calcium disturbances.

Table 3. Postoperative biochemical predictors of hypocalcemia

Biochemical parameter	Hypocalcemia (n=62)	Normocalcemia (n=138)	p-value
Early postoperative PTH, pg/mL	10.8 ± 6.4	28.6 ± 12.7	**<0.001**
Postoperative PTH <15 pg/mL	45 (72.6%)	24 (17.4%)	**<0.001**
PTH decline >60% from baseline	43 (69.4%)	26 (18.8%)	**<0.001**
6-hour corrected calcium, mg/dL	8.05 ± 0.39	8.71 ± 0.42	**<0.001**
24-hour corrected calcium, mg/dL	7.71 ± 0.43	8.62 ± 0.45	**<0.001**
Postoperative magnesium <1.7 mg/dL	19 (30.6%)	14 (10.1%)	**<0.001**
Symptomatic hypocalcemia	28 (45.2%)	0	**<0.001**
IV calcium required	12 (19.4%)	0	**<0.001**

Interpretation: Early postoperative PTH showed a strong association with subsequent hypocalcemia. Patients developing hypocalcemia had substantially lower postoperative PTH (10.8 vs 28.6 pg/mL) and calcium concentrations. A postoperative PTH <15 pg/mL and a >60% decline from baseline were markedly more frequent in the hypocalcemia group. These findings support early postoperative PTH and its percentage decline as potentially valuable components of a prediction model.

Table 4. Multivariable logistic regression analysis of independent predictors of postoperative hypocalcemia

Independent predictor	Adjusted OR	95% CI	p-value
Female sex	2.18	1.02–4.66	**0.044**
Vitamin D <20 ng/mL	2.42	1.21–4.86	**0.013**
Preoperative calcium <9.0 mg/dL	2.37	1.12–5.01	**0.024**
Central neck dissection	2.51	1.19–5.29	**0.016**
Inadvertent parathyroidectomy	3.46	1.08–11.09	**0.037**
Postoperative PTH <15 pg/mL	5.84	2.66–12.82	**<0.001**
PTH decline >60%	3.71	1.70–8.11	**0.001**

Interpretation: After adjustment for potential confounding variables, postoperative PTH <15 pg/mL was the strongest independent predictor of postoperative hypocalcemia, increasing the odds approximately 5.8-fold. A PTH decline >60%, inadvertent parathyroidectomy, central neck dissection, vitamin D deficiency, low preoperative calcium, and female sex also remained significant independent predictors. Thus, the final model incorporated factors contributed by clinical assessment, biochemical evaluation, and surgical findings rather than relying on a single postoperative laboratory measurement.

Table 5. Predictive performance of individual parameters and the multidisciplinary risk-prediction model

Prediction method	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Preoperative calcium alone	0.69 (0.61–0.77)	66.1%	65.2%	46.0%	81.1%
Vitamin D alone	0.62 (0.54–0.70)	56.5%	67.4%	43.8%	77.5%
Postoperative PTH <15 pg/mL	0.78 (0.71–0.85)	72.6%	82.6%	65.2%	87.0%
PTH decline >60%	0.75 (0.68–0.82)	69.4%	81.2%	62.3%	85.5%
Multidisciplinary prediction model	**0.89 (0.84–0.94)**	**83.9%**	**84.8%**	**71.2%**	**92.1%**

Interpretation: Postoperative PTH alone demonstrated good predictive ability (AUC 0.78), but the multidisciplinary model incorporating clinical, biochemical, and surgical predictors showed substantially better discrimination, with an AUC of 0.89 (95% CI 0.84–0.94). At the selected probability threshold, the model achieved 83.9% sensitivity, 84.8% specificity, and a high negative predictive value of 92.1%. The high NPV indicates that the model may be particularly useful for identifying low-risk patients who could potentially undergo less intensive biochemical monitoring and earlier discharge, subject to clinical assessment and prospective validation.

Overall Results

Among 200 patients undergoing total thyroidectomy, 62 (31.0%) developed postoperative hypocalcemia. Female sex, vitamin D deficiency, low preoperative calcium, central neck dissection, inadvertent parathyroidectomy, low postoperative PTH, and a marked postoperative PTH decline were independently associated with hypocalcemia. Postoperative PTH <15 pg/mL was the strongest individual predictor (aOR 5.84). However, combining clinical, biochemical, and surgical variables produced superior predictive performance (AUC 0.89) compared with individual biochemical parameters.

DISCUSSION

The present prospective study evaluated clinical, biochemical, and surgical predictors of postoperative hypocalcemia and developed a multidisciplinary risk-prediction model among 200 patients undergoing total thyroidectomy. Postoperative hypocalcemia occurred in 62 patients (31.0%), indicating that approximately one-third of patients experienced biochemical or clinically significant calcium disturbance following surgery. This frequency lies within the broad range reported internationally. Noureldine et al., in a study of 304 patients undergoing total thyroidectomy, reported 68 patients with mild and 91 with significant hypocalcemia, corresponding to an overall biochemical hypocalcemia burden exceeding 50% when both categories were considered.[8] Their study emphasized that differences in biochemical thresholds and severity classifications considerably influence reported postoperative hypocalcemia rates.

Female sex was significantly associated with postoperative hypocalcemia in the present study (83.9% vs 65.9%; p=0.009) and remained independently predictive after adjustment (aOR 2.18; 95% CI 1.02–4.66; p=0.044). Noureldine et al. similarly reported female proportions of 76% among patients with mild hypocalcemia and 79% among those with significant hypocalcemia, compared with 60% among normocalcemic patients, and identified female sex as an independent predictor.[8] The similarity between these findings supports the inclusion of sex as one component of a multivariable risk model rather than considering postoperative PTH alone. Vitamin D deficiency (<20 ng/mL) was present in 56.5% of patients with hypocalcemia compared with 32.6% of normocalcemic patients (p=0.001) and remained independently associated with postoperative hypocalcemia (aOR 2.42; p=0.013). Kirkby-Bott et al., in a prospective series of 166 total thyroidectomies, reported hypocalcemia rates of 32% in patients with vitamin D <10 ng/mL, 24% with intermediate levels, and 13% in those with vitamin D >20 ng/mL.[9] Their findings support the association observed in the present study and suggest that inadequate vitamin D reserve may impair the physiological ability to maintain serum calcium after an acute postoperative reduction in parathyroid function. Indian evidence also supports the relevance of vitamin D assessment. Tripathi et al. demonstrated a positive relationship between preoperative vitamin D concentrations and early postoperative serum calcium among patients undergoing thyroid surgery, indicating that vitamin D deficiency may contribute to post-thyroidectomy calcium disturbances.[16]

This finding is particularly relevant in the Indian setting, where vitamin D deficiency is frequently encountered and may modify the postoperative biochemical response following parathyroid manipulation. Nevertheless, the literature is not completely uniform: Griffin et al. evaluated 121 patients and reported transient biochemical hypocalcemia in 24%, but found no significant association between vitamin D level and postoperative hypocalcemia.[13] The conflicting evidence supports the present study's strategy of incorporating vitamin D into a multivariable model rather than using it as an isolated predictor. Preoperative calcium was significantly lower among patients developing hypocalcemia (9.02 ± 0.41 vs 9.31 ± 0.39 mg/dL; p<0.001), and a preoperative calcium concentration <9.0 mg/dL independently increased the odds of postoperative hypocalcemia (aOR 2.37; p=0.024). This finding indicates that patients beginning surgery with relatively limited calcium reserve may be less capable of compensating for transient postoperative impairment of PTH secretion. The predictive performance of preoperative calcium alone was nevertheless modest in the present study (AUC 0.69), suggesting that baseline calcium should complement rather than replace postoperative PTH-based assessment.

Hypomagnesemia was another significant biochemical factor, being observed preoperatively in 25.8% of hypocalcemic patients compared with 9.4% of normocalcemic patients (p=0.002). Postoperative magnesium <1.7 mg/dL was also significantly more frequent in patients developing hypocalcemia (30.6% vs 10.1%; p<0.001). Magnesium deficiency may contribute to impaired PTH secretion and reduced peripheral responsiveness to PTH, thereby aggravating postoperative calcium disturbances. These findings demonstrate the potential value of including magnesium assessment in a multidisciplinary biochemical evaluation rather than restricting postoperative surveillance to calcium alone. Surgical complexity had a substantial influence on hypocalcemia. Central neck dissection was performed in 38.7% of hypocalcemic patients compared with 19.6% of normocalcemic patients (p=0.004) and remained an independent predictor (aOR 2.51; p=0.016). Chisholm et al., in a systematic review and meta-analysis involving 1,132 patients, found that adding central neck dissection to thyroidectomy produced one additional case of temporary hypocalcemia for approximately every 7.7 central neck dissections performed.[11] This supports the present finding that more extensive cervical surgery increases the risk of transient parathyroid dysfunction.

The number and preservation of parathyroid glands were also clinically important. Identification and preservation of three or more parathyroid glands were less frequent among patients developing hypocalcemia (56.5% vs 76.8%; p=0.003), whereas inadvertent parathyroidectomy occurred in 16.1% of hypocalcemic patients compared with only 3.6% of normocalcemic patients (p=0.003). Inadvertent parathyroidectomy remained independently associated with hypocalcemia (aOR 3.46; 95% CI 1.08–11.09; p=0.037). Noureldine et al. similarly demonstrated progressively lower postoperative PTH values with each parathyroid gland inadvertently removed or requiring autotransplantation.[8] These observations reinforce the importance of meticulous identification and preservation of viable parathyroid tissue during total thyroidectomy. Parathyroid autotransplantation was performed in 22.6% of patients who developed hypocalcemia compared with 9.4% of normocalcemic patients (p=0.011).

Palazzo et al. demonstrated that temporary postoperative hypocalcemia was related to the number of parathyroid glands requiring autotransplantation, although long-term parathyroid function was not adversely affected.[12] Thus, the association between autotransplantation and early hypocalcemia probably reflects intraoperative compromise of parathyroid vascularity rather than failure of autotransplantation itself. The most prominent biochemical difference in the present study involved early postoperative PTH. Mean postoperative PTH was 10.8 ± 6.4 pg/mL in hypocalcemic patients compared with 28.6 ± 12.7 pg/mL in normocalcemic patients (p<0.001). A postoperative PTH <15 pg/mL was present in 72.6% of hypocalcemic patients compared with 17.4% of normocalcemic patients and emerged as the strongest independent predictor (aOR 5.84; 95% CI 2.66–12.82; p<0.001). Noureldine et al. similarly demonstrated that every 10-pg/mL increase in postoperative PTH was associated with a 43% reduction in the risk of significant hypocalcemia, confirming the strong inverse relationship between early PTH and subsequent calcium decline.[8]

The percentage decline in PTH provided additional predictive information. A decline >60% occurred in 69.4% of hypocalcemic patients compared with 18.8% of normocalcemic patients (p<0.001) and remained independently predictive (aOR 3.71; p=0.001). Cannizzaro et al. reported that among patients with an iPTH decline greater than approximately 55.7%, hypocalcemia occurred in 52%, whereas only 11.7% of patients with a smaller PTH decline developed hypocalcemia.[10] This closely supports the >60% threshold used in the present study and demonstrates that relative PTH decline may provide information beyond the absolute postoperative PTH concentration. White et al. also demonstrated that a 1-hour postoperative PTH measurement predicted symptomatic hypocalcemia, supporting the usefulness of early PTH measurement for rapid risk stratification.[14] Payne et al., in a prospective protocol involving 95 total thyroidectomy patients, used PTH and corrected calcium at 1 and 6 hours and reported a reduction in transient hypocalcemia from 28% to 9%, together with an approximately 10-hour reduction in mean hospital stay.[17]

These findings demonstrate the practical value of early biochemical prediction for supplementation and discharge planning. However, early PTH should not be interpreted without clinical context. Sahli et al. reported that a single 1-hour postoperative PTH measurement had limited sensitivity in their cohort and concluded that it did not reliably predict hypocalcemia when used alone.[15] This variation among studies may result from differences in assay platforms, timing, cut-off values, calcium supplementation protocols, patient characteristics, and surgical techniques. The present findings therefore support combining postoperative PTH with preoperative biochemical and operative factors rather than relying solely on a single PTH threshold. This concept was demonstrated by the predictive-performance analysis in the present study. Preoperative calcium alone produced an AUC of 0.69, vitamin D alone an AUC of 0.62, postoperative PTH <15 pg/mL an AUC of 0.78, and a >60% PTH decline an AUC of 0.75. In contrast, the multidisciplinary model incorporating clinical, biochemical, and surgical variables achieved an AUC of 0.89 (95% CI 0.84–0.94), with 83.9% sensitivity, 84.8% specificity, 71.2% PPV, and 92.1% NPV.

These findings are strongly supported by recent prediction-model research. Muller et al. developed and validated a multivariable machine-learning algorithm incorporating intraoperative PTH and clinical variables in 610 derivation and 118 validation patients. Postoperative hypocalcemia occurred in 16.4% and 22.0%, respectively, and their model achieved an AUC of 0.902 in the derivation cohort and 0.928 in the validation cohort.[18] The AUC of 0.89 observed in the present multidisciplinary model therefore approaches the discrimination achieved by this externally tested contemporary prediction approach. The high negative predictive value of 92.1% in the present model is particularly clinically relevant because a prediction tool for post-thyroidectomy hypocalcemia should reliably identify patients at very low risk. Patients classified as low risk could potentially undergo less intensive biochemical monitoring and earlier discharge, whereas those predicted to be at high risk could receive closer calcium surveillance and timely calcium and calcitriol supplementation. Muller et al.

similarly demonstrated that a low prediction threshold provided 92% sensitivity, while a high threshold achieved approximately 90% specificity, illustrating how multivariable risk prediction can be translated into individualized clinical pathways.[18]

Overall, the present study demonstrated that postoperative hypocalcemia following total thyroidectomy was multifactorial. Female sex, vitamin D deficiency, lower preoperative calcium, central neck dissection, inadvertent parathyroidectomy, postoperative PTH <15 pg/mL, and a PTH decline >60% emerged as independent predictors. Postoperative PTH was the strongest individual predictor; however, the superior AUC and high negative predictive value of the multidisciplinary model indicate that integrating patient-related, biochemical, and surgical information provides better individualized risk estimation than any single parameter. Such a model could potentially support risk-based calcium supplementation, postoperative monitoring, and safe discharge following total thyroidectomy, although internal validation and subsequent external validation would be required before routine clinical implementation.

CONCLUSION

The present prospective observational study demonstrated that postoperative hypocalcemia remains a common complication following total thyroidectomy, occurring in 31.0% (62/200) of patients. The development of hypocalcemia was influenced by a combination of patient-related, biochemical, and surgical factors, supporting a multidisciplinary approach to postoperative risk prediction. Early postoperative biochemical assessment showed that patients who developed hypocalcemia had significantly lower postoperative PTH and corrected calcium levels. Postoperative PTH <15 pg/mL and a decline in PTH >60% from the preoperative level demonstrated particularly strong associations with hypocalcemia. On multivariable analysis, female sex, vitamin D deficiency, preoperative calcium <9.0 mg/dL, central neck dissection, inadvertent parathyroidectomy, postoperative PTH <15 pg/mL, and PTH decline >60% emerged as independent predictors of postoperative hypocalcemia. Among these variables, postoperative PTH <15 pg/mL was the strongest individual predictor, with an adjusted odds ratio of 5.84. The multidisciplinary risk-prediction model combining clinical, biochemical, and surgical parameters demonstrated superior predictive performance, with an AUC of 0.89 (95% CI 0.84–0.94), sensitivity of 83.9%, specificity of 84.8%, and negative predictive value of 92.1%. This performance was better than that of preoperative calcium, vitamin D, postoperative PTH, or percentage PTH decline when considered individually.

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