

FREQUENCY OF HYPOCALCEMIA IN MULTINODULAR GOITRE PATIENTS UNDERGOING TOTAL THYROIDECTOMY

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ABSTRACT

Background: Postoperative hypocalcemia is a clinically important complication of total thyroidectomy that may prolong biochemical monitoring, delay discharge, and necessitate calcium and vitamin D therapy.

Objective: To determine the frequency of early postoperative hypocalcemia and evaluate associated demographic, clinical, histopathological, and biochemical factors among patients with multinodular goitre undergoing total thyroidectomy.

Methods: This prospective observational study included 125 patients aged 18–60 years undergoing total thyroidectomy at ENT Unit 1, Jinnah Hospital, Lahore for the duration of three months, from March 02, 2026 to June 02, 2026. Pakistan. Demographic, clinical, operative, histopathological, serum calcium, parathyroid hormone (PTH), and hospital-stay data were recorded. Early postoperative hypocalcemia was defined as serum calcium <8.5 mg/dL at 24 hours. Group comparisons, crude odds ratios, and an exploratory adjusted logistic regression analysis were performed.

Results: Early postoperative hypocalcemia occurred in 19 of 125 patients (15.2%; 95% CI, 10.0%–22.5%). Patients with hypocalcemia were younger than normocalcemic patients (37.74 ± 8.93 vs 42.81 ± 9.38 years; $p=0.031$). Thyroiditis was associated with higher crude odds of hypocalcemia (OR=3.62, 95% CI 1.16–11.29; $p=0.032$). The hypocalcemia group had lower serum calcium at 24 hours and one week, lower postoperative PTH, and longer hospital stay (all $p<0.001$). Postoperative PTH remained inversely associated with hypocalcemia in exploratory adjusted analysis (adjusted OR=0.587, 95% CI 0.433–0.795; $p=0.001$).

Conclusion: Early postoperative biochemical hypocalcemia occurred in approximately one in six patients. Lower postoperative PTH showed a strong inverse association with hypocalcemia, while thyroiditis was associated with increased crude odds. These findings support focused early biochemical surveillance after total thyroidectomy.

KEYWORDS: Multinodular goitre; total thyroidectomy; hypocalcemia; parathyroid hormone; thyroiditis; postoperative complications.

INTRODUCTION

Multinodular goitre is characterized by enlargement of the thyroid gland with multiple nodules and may remain asymptomatic or present with neck swelling, compressive symptoms, dysphagia, dyspnea, voice change, thyroid dysfunction, or suspicion of malignancy. Surgery is commonly considered for large or symptomatic goitres, retrosternal extension, recurrent disease, or suspicious nodules; total or near-total thyroidectomy reduces residual diseased tissue and recurrence but carries recognized perioperative risks [10,11].

Hypocalcemia is among the most frequent metabolic complications after total thyroidectomy. It usually reflects transient or sustained impairment of parathyroid function related to manipulation, edema, devascularization, thermal injury, inadvertent parathyroid excision, or other disruption of parathyroid integrity [3-6,23]. Clinical manifestations range from asymptomatic biochemical hypocalcemia to perioral numbness, paresthesia, muscle cramps, carpopedal spasm, tetany, seizures, and cardiac rhythm disturbances. Even transient biochemical abnormalities can increase monitoring requirements, supplementation needs, and length of hospital stay [16-18]. Reported rates vary substantially because studies differ in patient selection, thyroid pathology, extent of surgery, surgical technique, biochemical threshold, timing of calcium measurement, and whether total, albumin-corrected, or ionized calcium is used [3-5,12]. Meta-analytic evidence has identified several potential risk factors, including female sex, thyroid malignancy, thyroiditis, vitamin D deficiency, hypomagnesemia, central neck dissection, inadvertent parathyroidectomy, and lower perioperative PTH concentrations [3,4]. Pakistani studies have likewise reported variable frequencies of postoperative hypocalcemia, reflecting differences in case mix and definitions [1,2,7,9,10].

Parathyroid hormone has a short circulating half-life and can therefore provide an early biochemical indication of postoperative parathyroid dysfunction. Contemporary studies and systematic reviews support the association

of early postoperative PTH or the perioperative change in PTH with subsequent hypocalcemia, while emphasizing that predictive performance depends on sampling time, threshold, and outcome definition [5,12-15,22,24]. Postoperative PTH is therefore best interpreted as an early postoperative biomarker rather than a preoperative patient characteristic.

Because local estimates and associated factors remain heterogeneous, institution-specific data can help refine postoperative surveillance and identify patients who may require closer biochemical observation. This study therefore aimed to determine the frequency of early postoperative hypocalcemia in patients with multinodular goitre undergoing total thyroidectomy and to evaluate its associations with demographic and clinical factors, histopathology, perioperative calcium and PTH, and length of hospital stay.

MATERIALS AND METHODS

Study design and setting

A prospective observational study was conducted at ENT Unit 1, Jinnah Hospital, Lahore, Pakistan, over a period of three months from March 2, 2026 to June 2, 2026. The study evaluated the frequency of early postoperative hypocalcemia and its associations with demographic, clinical, operative, histopathological, and biochemical factors in patients with multinodular goitre undergoing total thyroidectomy. The research protocol was developed in conjunction with FCPS-II training and was registered with the Research and Training Monitoring Cell of the College of Physicians and Surgeons Pakistan under registration number CPSP/REU/ENT-2022-055-1500.

Participants and eligibility

Patients aged 18–60 years with clinically and radiologically diagnosed multinodular goitre who were scheduled for total thyroidectomy were eligible. Multinodular goitre was defined clinically and radiologically by an enlarged thyroid gland containing multiple nodules. Cytological assessment was performed when clinically indicated. Patients with previous thyroid and/or parathyroid surgery, chronic renal failure with potential to alter calcium metabolism, or pregnancy/lactation were excluded. Written informed consent was obtained from all participants.

Sampling and sample-size estimation

Consecutive non-probability sampling was used. Sample size was calculated for estimation of a single population proportion using the World Health Organization sample-size approach. An anticipated postoperative hypocalcemia frequency of 10% and a 95% confidence level were used. For a sample of 125 patients, the corresponding absolute precision is approximately 5.3%, based on $n = Z^2 p(1-p)/d^2$. Consecutive eligible patients were enrolled until the target sample was achieved.

Data collection and study variables

Data were recorded on a predefined structured proforma. Baseline variables included age, sex, residence, weight, height, body mass index (BMI), duration of goitre, nodule-size category, compressive symptoms, clinical history, and preoperative calcium or vitamin D use. BMI was calculated as weight in kilograms divided by height in metres squared (kg/m^2). The operative-technique category was recorded from the surgical record. Thyroiditis and malignant histopathology were determined from postoperative histopathological findings.

Outcome assessment

The primary outcome was early postoperative hypocalcemia, defined as serum calcium <8.5 mg/dL at 24 hours after total thyroidectomy. Serum calcium was assessed preoperatively, 24 hours postoperatively, and at one-week follow-up to describe the early biochemical course. Preoperative and early postoperative PTH levels were recorded. Postoperative PTH was treated as an early postoperative biochemical marker associated with hypocalcemia rather than as a preoperative risk factor. Postoperative hospital stay was recorded in days as an indicator of early clinical recovery.

All patients underwent total thyroidectomy according to the approach selected by the treating team. Early postoperative clinical and biochemical monitoring followed routine hospital practice. Patients who developed hypocalcemia were managed according to their biochemical findings and clinical assessment. The study was observational and did not alter routine surgical care.

To improve measurement consistency, the same predefined definitions and data-collection proforma were used for all participants, and blood samples were obtained at the stated perioperative time points and processed by the hospital laboratory. Potential confounding or effect-modifying variables considered in the analysis included age, sex, BMI, duration of goitre, nodule size, compressive symptoms, thyroiditis, malignant histopathology, operative-technique category, preoperative calcium, and preoperative calcium/vitamin D use.

Statistical analysis

Data were entered and analyzed using IBM SPSS Statistics version 25.0. Continuous variables were summarized as mean $\pm$ standard deviation (SD), and categorical variables as frequency and percentage. Continuous variables were compared between hypocalcemic and normocalcemic groups using independent-samples t tests. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test when expected cell counts were small. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were reported for categorical comparisons. The 95% CI for the primary hypocalcemia proportion was calculated using the Wilson score method. A two-sided p value <0.05 was considered statistically significant.

Binary logistic regression was used as an exploratory adjusted analysis of factors associated with postoperative hypocalcemia. Because only 19 hypocalcemia events occurred, adjusted estimates were interpreted cautiously with emphasis on direction, magnitude, and precision rather than on development of a definitive prediction model. Analyses were performed on the complete dataset.

Ethical considerations

The study was done after obtaining approval from the institutional and postgraduate training authorities. Informed written consent was taken from all participants, and confidentiality was maintained by keeping data anonymous and access restricted for research team only. Study involved observation of routine perioperative care and did not expose participants to any experimental intervention.

RESULTS

A total of 125 patients with multinodular goitre undergoing total thyroidectomy were included in the analysis. The mean age was 42.04 ± 9.45 years, mean BMI was 26.75 ± 4.36 kg/m², and mean duration of goitre was 4.93 ± 2.24 years. Women comprised 98 of 125 participants (78.4%).

Early postoperative hypocalcemia occurred in 19 patients, giving a frequency of 15.2% (95% CI 10.0%–22.5%); 106 patients (84.8%) remained normocalcemic (Figure 1). Patients who developed hypocalcemia were on average 5.07 years younger than those who remained normocalcemic (37.74 ± 8.93 vs 42.81 ± 9.38 years; mean difference -5.07 years, 95% CI -9.66 to -0.48 ; $p=0.031$). BMI and duration of goitre did not differ significantly between groups.

Table 1. Continuous baseline characteristics according to postoperative hypocalcemia status

Variable	Overall n=125	No hypocalcemia n=106	Hypocalcemia n=19	Mean difference (95% CI)	p value
Age, years	42.04 ± 9.45	42.81 ± 9.38	37.74 ± 8.93	-5.07 (-9.66 to -0.48)	0.031
Body mass index, kg/m ²	26.75 ± 4.36	26.47 ± 4.23	28.28 ± 4.85	1.81 (-0.32 to 3.94)	0.096
Duration of goitre, years	4.93 ± 2.24	4.96 ± 2.32	4.76 ± 1.78	-0.20 (-1.31 to 0.91)	0.724

Values are mean $\pm$ SD. Mean differences are hypocalcemia minus no-hypocalcemia. P values are from independent-samples t tests. CI, confidence interval.

When age was categorized, hypocalcemia occurred in 12 of 55 patients aged 18–40 years (21.8%) and 7 of 70 aged 41–60 years (10.0%). The crude odds were higher in the younger group, but the categorical comparison did not reach statistical significance (OR=2.51, 95% CI 0.92–6.89; $p=0.068$).

Table 2. Demographic, clinical, operative, and histopathological factors associated with postoperative hypocalcemia

Variable/category	Total, n	Hypocalcemia, n (%)	Crude OR (95% CI)	p value
Age group: 41–60 years	70	7 (10.0)	1.00	
Age group: 18–40 years	55	12 (21.8)	2.51 (0.92–6.89)	0.068
Sex: Male	27	3 (11.1)	1.00	
Sex: Female	98	16 (16.3)	1.56 (0.42–5.81)	0.763
Goitre duration: <5 years	72	12 (16.7)	1.00	
Goitre duration: ≥ 5 years	53	7 (13.2)	0.76 (0.28–2.09)	0.594
Compressive symptoms: Absent	90	15 (16.7)	1.00	
Compressive symptoms: Present	35	4 (11.4)	0.65 (0.20–2.10)	0.464
Thyroiditis: Absent	107	13 (12.1)	1.00	
Thyroiditis: Present	18	6 (33.3)	3.62 (1.16–11.29)	0.032
Preoperative calcium/vitamin D use: Absent	100	14 (14.0)	1.00	
Preoperative calcium/vitamin D use: Present	25	5 (20.0)	1.54 (0.50–4.76)	0.533
Histopathology: Benign	107	14 (13.1)	1.00	
Histopathology: Malignant	18	5 (27.8)	2.55 (0.79–8.27)	0.149
Operative technique: Other documented techniques	33	5 (15.2)	1.00	
Operative technique: Conventional total thyroidectomy	92	14 (15.2)	1.01 (0.33–3.05)	1.000

Percentages are calculated within each row. Odds ratios compare each category with the stated reference category. Pearson's chi-square test was used where expected cell counts were adequate; Fisher's exact test was

used for sex, thyroiditis, preoperative supplementation, histopathology, and operative-technique comparisons. CI, confidence interval; OR, odds ratio.

Thyroiditis was the only categorical factor with a statistically significant crude association. Hypocalcemia developed in 6 of 18 patients with thyroiditis (33.3%) versus 13 of 107 without thyroiditis (12.1%), corresponding to 3.62-fold higher crude odds (95% CI 1.16–11.29; Fisher's exact $p=0.032$). Malignant histopathology showed a numerically higher frequency than benign histopathology (27.8% vs 13.1%), but the estimate was imprecise and not statistically significant (OR=2.55, 95% CI 0.79–8.27; $p=0.149$). Sex, duration of goitre, compressive symptoms, preoperative calcium/vitamin D use, and operative-technique category were also not significantly associated with hypocalcemia.

Preoperative serum calcium was essentially identical in the two groups (9.34 ± 0.38 vs 9.34 ± 0.33 mg/dL; $p=0.986$). At 24 hours, the mean serum calcium was 0.92 mg/dL lower in the hypocalcemia group (8.17 ± 0.20 vs 9.09 ± 0.30 mg/dL; $p<0.001$). Because the 24-hour calcium value defined the primary outcome, this comparison describes the magnitude of separation between groups rather than an independent risk association. At one week, mean calcium remained lower in the hypocalcemia group (8.54 ± 0.29 vs 9.17 ± 0.35 mg/dL; mean difference -0.63 mg/dL, 95% CI -0.80 to -0.46 ; $p<0.001$) (Figure 2).

Preoperative PTH was lower in patients who subsequently developed hypocalcemia, although this difference was not statistically significant (34.98 ± 8.38 vs 39.08 ± 9.08 ; $p=0.069$). In contrast, postoperative PTH was substantially lower in the hypocalcemia group (10.22 ± 3.46 vs 27.15 ± 9.54 ; mean difference -16.93 , 95% CI -21.33 to -12.53 ; $p<0.001$). Patients with hypocalcemia stayed in hospital an average of 1.13 days longer (4.05 ± 0.71 vs 2.92 ± 0.94 days; 95% CI 0.68 – 1.58 ; $p<0.001$).

Table 3. Perioperative biochemical profile and postoperative hospital stay

Variable	Overall n=125	No hypocalcemia n=106	Hypocalcemia n=19	Mean difference (95% CI)	p value
Preoperative calcium, mg/dL	9.34 ± 0.34	9.34 ± 0.33	9.34 ± 0.38	0.00 (-0.17 to 0.17)	0.986
Calcium at 24 hours, mg/dL	8.95 ± 0.43	9.09 ± 0.30	8.17 ± 0.20	-0.92 (-1.06 to -0.78)	<0.001
Calcium at one week, mg/dL	9.07 ± 0.41	9.17 ± 0.35	8.54 ± 0.29	-0.63 (-0.80 to -0.46)	<0.001
Preoperative PTH	38.46 ± 9.07	39.08 ± 9.08	34.98 ± 8.38	-4.10 (-8.53 to 0.33)	0.069
Postoperative PTH	24.58 ± 10.78	27.15 ± 9.54	10.22 ± 3.46	-16.93 (-21.33 to -12.53)	<0.001
Hospital stay, days	3.09 ± 0.99	2.92 ± 0.94	4.05 ± 0.71	1.13 (0.68 – 1.58)	<0.001

Values are mean $\pm$ SD. Mean differences are hypocalcemia minus no-hypocalcemia. P values are from independent-samples *t* tests. CI, confidence interval; PTH, parathyroid hormone.

In the exploratory adjusted logistic regression analysis, postoperative PTH retained a statistically significant inverse association with postoperative hypocalcemia. Each one-unit increase in postoperative PTH was associated with lower adjusted odds of hypocalcemia (adjusted OR=0.587, 95% CI 0.433–0.795; $p=0.001$). Given the 19 outcome events, this estimate was interpreted as hypothesis-generating rather than as a definitive prediction model.

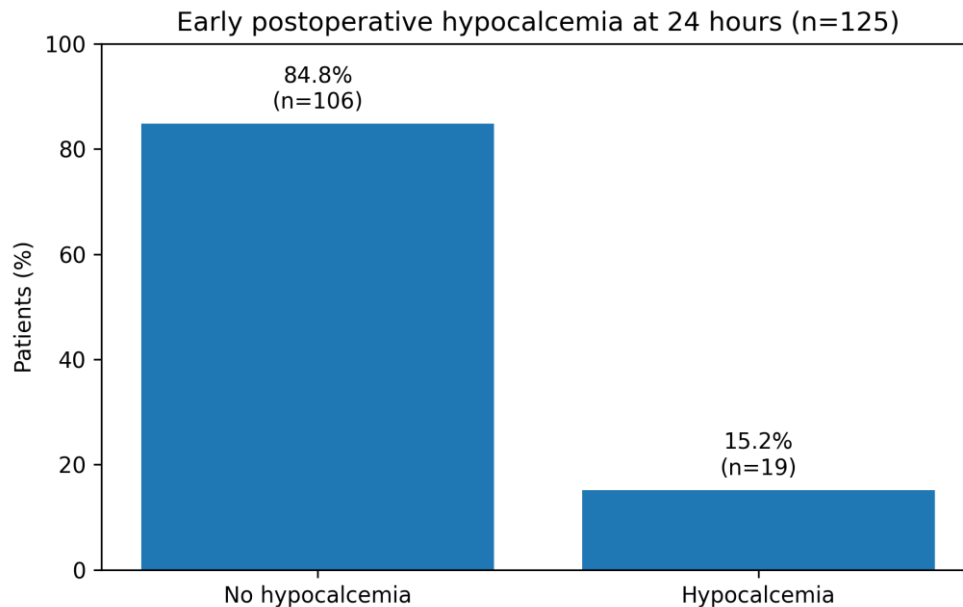


Figure 1. Frequency of early postoperative hypocalcemia at 24 hours after total thyroidectomy.

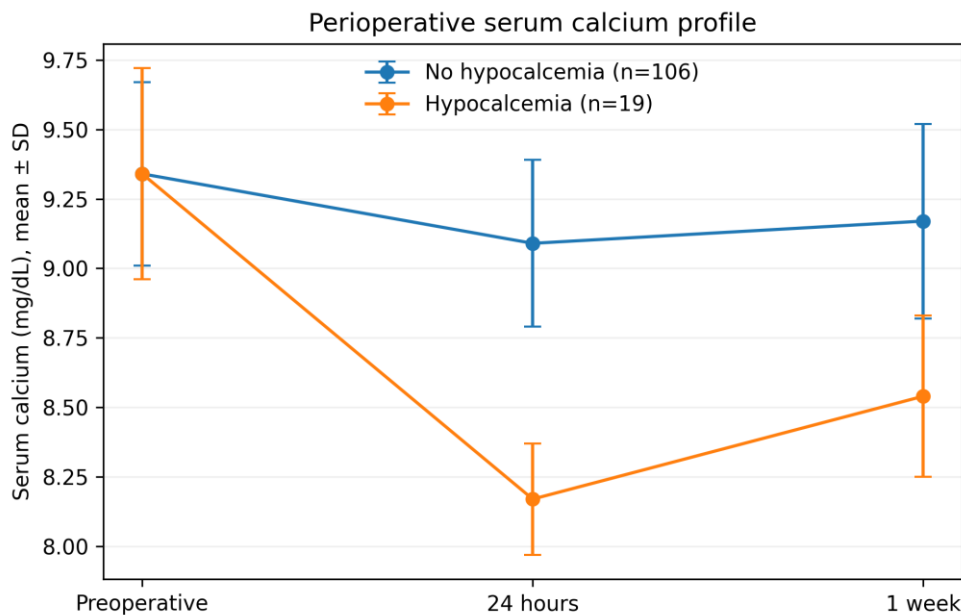


Figure 2. Mean serum calcium concentrations ($\pm$ SD) preoperatively, at 24 hours, and at one week according to postoperative hypocalcemia status.

DISCUSSION

This study found an early postoperative biochemical hypocalcemia frequency of 15.2% after total thyroidectomy for multinodular goitre. The estimate is lower than several Pakistani reports, including studies that reported approximately 28% or higher frequencies after total or near-total thyroidectomy [2,7,10], and lower than the broad postoperative hypocalcemia burden reported in larger reviews [3-5]. Such differences are expected because incidence estimates are highly sensitive to thyroid pathology, extent of surgery, perioperative supplementation, biochemical threshold, timing of measurement, and whether biochemical or symptomatic outcomes are used [3-5,12]. The present study specifically defined the outcome using total serum calcium <8.5 mg/dL at 24 hours.

Preoperative calcium was essentially identical between groups, whereas the postoperative biochemical profile diverged substantially. The difference in 24-hour calcium is inherently linked to the study definition of hypocalcemia and should therefore be interpreted descriptively rather than as an independent risk association. More clinically informative was the persistence of a lower mean calcium concentration at one week among patients who were hypocalcemic at 24 hours. However, the one-week follow-up window addresses early biochemical recovery only and does not permit classification of long-term or permanent postoperative hypoparathyroidism, for which contemporary guidance uses substantially longer follow-up [15,23,24].

The strongest biochemical finding was the inverse association between postoperative PTH and hypocalcemia. Patients who developed hypocalcemia had markedly lower postoperative PTH, and postoperative PTH retained a significant association in the exploratory adjusted analysis. This finding is biologically coherent because parathyroid manipulation or vascular compromise during thyroidectomy can produce an early decline in PTH before or alongside a fall in serum calcium [12,23]. Recent evidence has consistently identified postoperative PTH, absolute PTH change, or percentage decline from baseline as useful early markers of postoperative parathyroid dysfunction [5,12-15,22,24]. Swift et al. [13] found that early absolute PTH values and change from baseline were associated with subsequent hypocalcemia, while Thakur et al. [14] demonstrated clinically useful early postoperative PTH discrimination at defined postoperative time points. The present study supports the same direction of association but did not evaluate a diagnostic cutoff or receiver-operating characteristic performance; therefore, its regression result should not be interpreted as establishing a threshold for discharge or supplementation.

Thyroiditis was associated with approximately 3.6-fold higher crude odds of hypocalcemia. This direction is consistent with meta-analytic evidence identifying thyroiditis as a risk factor for postoperative hypocalcemia [3]. Inflammatory change can increase fibrosis, tissue adherence, and technical difficulty around the thyroid capsule and parathyroid vascular supply. Nevertheless, only 18 patients in the current cohort had thyroiditis, and the confidence interval was wide. The finding is therefore best regarded as a clinically plausible association that merits confirmation rather than proof of an independent causal effect.

Age showed a mixed pattern. The mean age was significantly lower in the hypocalcemia group, but the comparison using 18–40 and 41–60 year categories did not reach statistical significance. Meta-analytic evidence has reported younger age among predictors of transient hypocalcemia in some populations [4], whereas other studies, including work focused on older adults, demonstrate substantial heterogeneity in age-related findings [8]. The current results illustrate the information loss that can occur when a continuous variable is dichotomized and do not support a specific age threshold for risk stratification.

Female sex and malignant histopathology were not statistically significant in this cohort, although the malignant group had a numerically higher hypocalcemia frequency. Larger evidence syntheses have associated female sex and thyroid malignancy with increased postoperative risk [3,4]. The absence of statistical significance in this study may reflect the limited number of events and the small malignant subgroup rather than definitive evidence of no association. Similarly, the operative-technique comparison showed identical hypocalcemia proportions across the broad categories used here; detailed operative factors such as parathyroid identification, inadvertent excision, central neck dissection, and preservation techniques are known to influence parathyroid outcomes [3,19,23].

Patients with hypocalcemia remained hospitalized approximately 1.13 days longer. This is clinically important because postoperative calcium disturbance can delay discharge through repeated biochemical testing, symptom surveillance, and adjustment of calcium or active vitamin D treatment. Recent randomized and meta-analytic evidence shows that perioperative calcium/vitamin D strategies can reduce biochemical or symptomatic hypocalcemia in selected settings, although protocols and outcomes remain heterogeneous [16-21]. The present observational study did not compare supplementation strategies, so it cannot determine whether any specific prophylactic regimen would shorten hospital stay in this population.

The study has several strengths: prospective enrollment, a clearly defined primary biochemical outcome, repeated calcium assessment at prespecified perioperative points, inclusion of perioperative PTH, and evaluation of demographic, clinical, histopathological, and recovery-related variables. The study also presents effect estimates and confidence intervals rather than relying solely on p values.

Important limitations should temper interpretation. This was a single-center study using consecutive non-probability sampling, which restricts generalizability. Only 19 hypocalcemia events occurred, limiting precision of subgroup estimates and the stability of multivariable analysis. Follow-up extended to one week, so the study addresses early biochemical hypocalcemia rather than persistent or permanent hypoparathyroidism. Several exploratory comparisons were performed, increasing the possibility of chance findings. Future studies should use multicenter recruitment, longer follow-up, prespecified parsimonious prediction models, and standardized calcium/PTH protocols incorporating clinically relevant biochemical and operative variables.

CONCLUSION

Early postoperative biochemical hypocalcemia occurred in 15.2% of patients with multinodular goitre undergoing total thyroidectomy. Lower postoperative PTH showed a strong inverse association with hypocalcemia, thyroiditis was associated with higher crude odds, and affected patients had a longer hospital stay. These findings support careful early biochemical surveillance after total thyroidectomy while larger, adequately powered studies are needed before adopting a formal PTH-based prediction or discharge algorithm.

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