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ORIGINAL ARTICLE

Predictors of severe postoperative hypocalcemia following parathyroidectomy for primary hyperparathyroidism: a retrospective cohort study

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ABSTRACT

Aims: Postoperative hypocalcemia is a common complication following parathyroidectomy for primary hyperparathyroidism (PHPT), ranging from transient, asymptomatic decreases in serum calcium to prolonged hungry bone syndrome (HBS). This study aimed to identify independent predictors of severe postoperative hypocalcemia using a composite clinicobiological definition and to assess the role of early postoperative parathyroid hormone (PTH) kinetics. **Patients and Methods:** We conducted a retrospective cohort study including 166 consecutive patients who underwent parathyroidectomy for PHPT between January 2019 and May 2025. Severe hypocalcemia within the first three postoperative days was defined as: (a) corrected serum calcium <70 mg/L; (b) calcium <75 mg/L associated with clinical symptoms (perioral or digital paresthesia, Trousseau's sign, muscle cramps, or confusion); or (c) requirement for intravenous calcium infusion. Preoperative, surgical, and early postoperative variables—including the percentage decrease in PTH from preoperative levels to postoperative day 1—were analyzed. Multivariate analysis was performed using Firth's logistic regression to reduce overfitting, with the model limited to three preselected variables. **Results:** Severe hypocalcemia occurred in 12 patients (7.2%), including 8 cases (4.8%) of hungry bone syndrome. Independent predictors were adenoma weight >2 g (OR = 4.0, 95% CI: 1.4–11.2; p = 0.008), bilateral neck exploration (OR = 3.5, 95% CI: 1.2–10.1; p = 0.02), and a >80% decrease in PTH from preoperative levels to postoperative day 1 (OR = 5.0, 95% CI: 1.7–14.5; p = 0.003). The optimal cut-off value for PTH reduction was 75% (AUC = 0.81). Preoperative vitamin D deficiency and osteoporosis were not independently associated with severe hypocalcemia after adjustment. **Conclusion:** Adenoma weight >2 g, bilateral neck exploration, and a >75% decrease in PTH by postoperative day 1 are independent predictors of severe hypocalcemia. Early postoperative PTH measurement is a simple and valuable tool for guiding prophylactic calcium and calcitriol supplementation.

Keywords: Primary hyperparathyroidism, postoperative hypocalcemia, hungry bone syndrome, parathyroidectomy, PTH kinetics.

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1. INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, with an estimated prevalence of 0.2–1.3% in the general population and a higher incidence among postmenopausal women [1]. The disease is characterized by excessive and often autonomous secretion of parathyroid hormone (PTH), leading to chronic hypercalcemia and complications including nephrolithiasis, osteoporosis, fractures, and neuropsychiatric symptoms [2]. Parathyroidectomy is the only curative treatment, achieving success rates above 95% in experienced centers [3].

Postoperative hypocalcemia remains a frequent complication after parathyroidectomy, occurring in 5–40% of patients depending on the definition and surgical extent [4]. This complication encompasses a spectrum of severity, from transient asymptomatic hypocalcemia to severe hypocalcemia requiring intravenous calcium supplementation and to hungry bone syndrome (HBS) – a profound and prolonged calcium drop due to rapid skeletal remineralization after removal of the source of excess PTH [5,6]. Prolonged hypocalcemia lasting more than six months may indicate permanent hypoparathyroidism. Identifying patients at risk for severe or prolonged hypocalcemia before surgery is crucial to tailor postoperative management, reduce hospital stay, and prevent complications [7].

Several predictors have been proposed, including high preoperative PTH, large adenoma weight, bilateral neck exploration, vitamin D deficiency, and bone involvement [8,9]. However, the role of early postoperative PTH kinetics (the percentage drop in PTH) has been less explored, and data from North African populations are scarce. Moreover, most studies define hypocalcemia solely by a biochemical threshold, ignoring clinical symptoms or therapeutic needs, which limits clinical relevance.

The present study was therefore designed to: (1) determine independent predictors of **severe** postoperative hypocalcemia using a composite definition that includes clinical and therapeutic criteria; (2) evaluate the predictive value of early postoperative PTH kinetics; and (3) propose a simple risk-stratification strategy.

2. PATIENTS AND METHODS

Study design and population

This retrospective, observational, single-center study included 166 consecutive patients who underwent parathyroidectomy for PHPT between January 2019 and December 2025 at the Department of General Surgery, EHS of Organ and Tissue Transplantation (T.O.T.), Blida, Algeria. Inclusion criteria were preoperative hypercalcemia with elevated or inappropriately normal intact PTH, histologically confirmed parathyroid adenoma, and availability of preoperative and postoperative calcium and PTH measurements. Exclusion criteria were secondary or tertiary hyperparathyroidism, parathyroid hyperplasia, and parathyroid carcinoma.

Ethical considerations

All patients provided written informed consent for the surgical procedure and for the use of their anonymized data for research purposes. The study was conducted in accordance with the Declaration of Helsinki.

Definitions

Severe postoperative hypocalcemia was defined as the presence of at least one of the following within the first three postoperative days: corrected serum calcium <70 mg/L (1.75 mmol/L); or corrected serum calcium <75 mg**/L** (1.87 mmol/L) with clinical symptoms (perioral or digital paresthesia, Trousseau's sign, muscle cramps, confusion); or Need for intravenous calcium infusion to treat symptoms or prevent complications.

Prolonged hypocalcemia was defined as serum calcium <80 mg/L persisting beyond six months after surgery.

Hungry bone syndrome (HBS) was defined as severe hypocalcemia (as above) associated with hypophosphatemia (< 25 mg/L) and elevated alkaline phosphatase (>2× upper normal limit) occurring within 72 hours after parathyroidectomy and requiring intravenous calcium for more than three days [6].

Bone involvement was assessed by dual-energy X-ray absorptiometry (DXA) to diagnose osteoporosis (T-score ≤ –2.5), as well as by clinical history of bone pain, pathological fractures, and the presence of brown tumors on imaging or histology.

Data collection

Preoperative variables included age, sex, BMI, intact PTH (ng/L), total serum calcium (mg/L), 24-hour urinary calcium (mg/24h), serum phosphorus (mg/L), 25-OH vitamin D (ng/mL), serum creatinine, estimated glomerular filtration rate (eGFR, CKD-EPI), DXA results (T-score), history of bone pain, pathological fractures, and brown tumors. Surgical variables included adenoma weight (g), type of surgery (targeted mini-cervicotomy vs. bilateral neck exploration), and operative time (minutes). Postoperative variables included serum calcium on days 1, 2, and 3 (mg/L), PTH on day 1 (ng/L), the percentage drop in PTH from preoperative to day 1, need for intravenous calcium, length of hospital stay, and calcium/vitamin D supplementation at six months.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or as median with interquartile range (IQR) for non-normally distributed data. Comparisons between patients with and without severe hypocalcemia were performed using Student's t-test,

Mann-Whitney U test, or χ^2 test as appropriate. To avoid overfitting given the limited number of events (12 severe hypocalcemia cases after applying the composite definition), we used Firth logistic regression (penalized maximum likelihood) and limited the model to three preselected clinically relevant variables: adenoma weight >2 g, bilateral neck exploration, and percentage PTH drop (dichotomized at the optimal cut-off). Variables with p<0.10 in univariate analysis were considered for inclusion. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A receiver operating characteristic (ROC) curve was constructed for the percentage drop in PTH, and the optimal cut-off was determined using the Youden index. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 26.

3. RESULTS

Prevalence and types of hypocalcemia

Among the 166 patients, severe hypocalcemia (composite definition) occurred in 12 patients (7.2%). Of these, 8 (4.8%) fulfilled criteria for hungry bone syndrome, and 5 (3.0%) had prolonged hypocalcemia lasting beyond six months. No patient developed permanent hypoparathyroidism or recurrent laryngeal nerve injury.

Univariate analysis

The comparison of variables between patients with and without severe hypocalcemia is presented in Table 1. Patients who developed severe hypocalcemia had significantly higher preoperative PTH (median 340 vs. 190 ng/L, p=0.01), lower vitamin D levels (median 10 vs. 20 ng/mL, p=0.007), larger adenomas (median weight 3.0 vs. 1.2 g, p<0.001), and more frequent bilateral neck exploration (58.3% vs. 14.9%, p<0.001). Bone involvement variables – osteoporosis (66.7% vs. 20.8%, p=0.001), bone pain (58.3% vs. 19.5%, p=0.004), pathological fractures (16.7% vs. 3.9%, p=0.04), and brown tumors (8.3% vs. 1.3%, p=0.04) – were all significantly associated with severe hypocalcemia. The percentage drop in PTH from preoperative to day 1 was significantly larger in hypocalcemic patients (median 90% vs. 75%, p<0.001), and day-1 PTH levels were lower (median 15 vs. 35 ng/L, p=0.002).

Table 1. Univariate comparison of patients with and without severe postoperative hypocalcemia (composite definition).

Variable	No severe hypocalcemia (n=154)	Severe hypocalcemia (n=12)	p
Age (years)	54.3 ± 12.5	57.2 ± 11.3	0.42
Female sex (%)	82.5	83.3	0.94
BMI (kg/m²)	25.8 ± 4.1	26.4 ± 4.0	0.62
Preoperative calcium (mg/L)	118 ± 14	127 ± 17	0.23
Preoperative PTH (ng/L)*	190 (120–280)	340 (200–480)	**0.01**
Vitamin D (ng/mL)*	20 (12–28)	10 (8–16)	**0.007**
24h urinary calcium (mg/24h)	288 ± 35	300 ± 40	0.48
Serum phosphorus (mg/L)	27.0 ± 8.5	23.5 ± 7.0	0.08
Osteoporosis (T-score ≤ –2.5)	32 (20.8%)	8 (66.7%)	**0.001**
Bone pain	30 (19.5%)	7 (58.3%)	**0.004**
Pathological fractures	6 (3.9%)	2 (16.7%)	**0.04**
Brown tumors	2 (1.3%)	1 (8.3%)	**0.04**
Adenoma weight (g)*	1.2 (0.8–2.2)	3.0 (1.8–4.5)	**<0.001**
Bilateral neck exploration	23 (14.9%)	7 (58.3%)	**<0.001**
Operative time (min)*	45 (35–55)	58 (45–70)	0.06
Day-1 PTH (ng/L)*	35 (20–55)	15 (9–25)	**0.002**
PTH drop (%)*	75 (65–85)	90 (85–95)	**<0.001**

**Median (IQR); other values are mean ± SD or n (%)*

Multivariate analysis

After Firth logistic regression with the three predefined variables (Table 2), independent predictors of severe postoperative hypocalcemia were: adenoma weight >2 g: OR = 4.0 (95% CI 1.4–11.2, p = 0.008), bilateral neck exploration: OR = 3.5 (95% CI 1.2–10.1, p = 0.02), and PTH drop >80% (preoperative to day 1): OR = 5.0 (95% CI 1.7–14.5, p = 0.003). Preoperative vitamin D deficiency (<20

ng/mL) and osteoporosis (T-score ≤ –2.5) were not significant after adjustment (p > 0.15) and were removed from the final model to avoid overfitting.

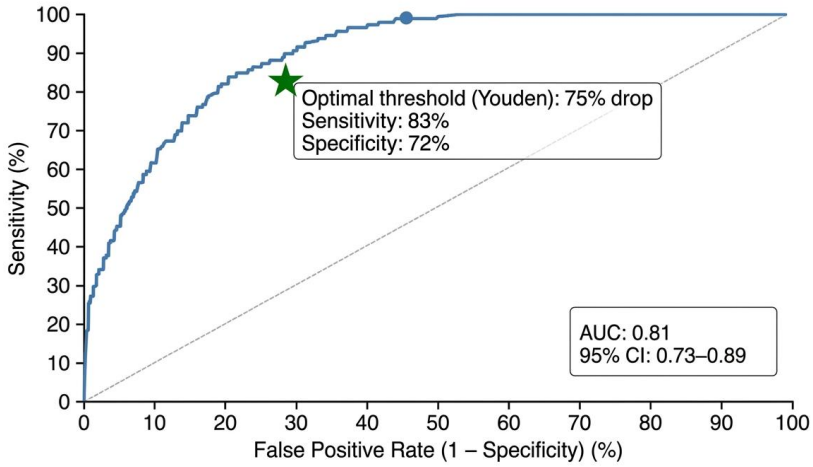
Table 2. Multivariate analysis for independent predictors of severe postoperative hypocalcemia.

Variable	Adjusted OR	95% CI	p
Adenoma weight >2 g	4.0	1.4 – 11.2	0.008
Bilateral neck exploration	3.5	1.2 – 10.1	0.02
PTH drop >80% (preop → day 1)	5.0	1.7 – 14.5	0.003

ROC curve for PTH drop

The ROC curve for the percentage drop in PTH (preoperative to day 1) gave an area under the curve (AUC) of 0.81 (95% CI 0.73–0.89), indicating good discriminative ability. The optimal cut-off determined by the Youden index was a 75% drop, which provided a sensitivity of 83% and a specificity of 72% for predicting severe hypocalcemia. Early postoperative PTH thus emerged as a valuable predictor, allowing early identification of patients at risk. **(**Figure 1).

Figure 1: ROC Curve for Percentage Drop in PTH for Predicting Severe Hypocalcemia



Graph illustrating the discriminative capacity of the PTH drop for the prediction of severe hypocalcemia (AUC = 0.81)

Figure 1. ROC curve of the percentage drop in PTH (preoperative to postoperative day 1) for predicting severe postoperative hypocalcemia.

Subgroup analysis

Table 3 shows the incidence of severe hypocalcemia according to risk factors. Adenoma weight ≥2 g was associated with a 2.8-fold higher risk (16.0% vs. 6.6%, p=0.04). Bilateral neck exploration increased risk 6.2-fold (28.6% vs. 6.1%, p<0.001). When both risk factors were present (bilateral exploration + adenoma ≥ 2 g), the incidence of severe hypocalcemia reached 45.5% (5/11), demonstrating an additive effect.

Table 3. Subgroup analysis – incidence of severe hypocalcemia according to risk factors.

Subgroup	n	Severe hypocalcemia n (%)	OR (95% CI)	p
Adenoma weight <2 g	91	6 (6.6%)	Reference	–
Adenoma weight ≥2 g	75	12 (16.0%)	2.8 (1.0–7.5)	0.04
Targeted mini-cervicotomy	131	8 (6.1%)	Reference	–
Bilateral neck exploration	35	10 (28.6%)	6.2 (2.2–17.3)	<0.001
Bilateral + adenoma <2 g	24	5 (20.8%)	–	–
Bilateral + adenoma ≥2 g	11	5 (45.5%)	–	–

4. DISCUSSION

This study demonstrates that after parathyroidectomy for PHPT, severe postoperative hypocalcemia – defined by a composite of biochemical, clinical, and therapeutic criteria – occurs in 7.2% of patients, with hungry bone syndrome in 4.8% and prolonged hypocalcemia in 3.0%. These figures are consistent with the 5–10% range reported in Western series [4,7]. The higher rate of HBS compared to some contemporary studies (2–5%) reflects the more advanced bone disease in our cohort: 66.7% of hypocalcemic patients had osteoporosis, 58.3% had bone pain, and 16.7% had pathological fractures. This pattern is typical of intermediate-resource countries where PHPT is often diagnosed at a symptomatic stage.

The independent predictors identified – adenoma weight > 2 g, bilateral neck exploration, and a >75% drop in PTH by day 1 – are easily measurable and clinically actionable.

Adenoma weight > 2 g increased the risk of severe hypocalcemia four-fold. Large adenomas are associated with higher PTH levels, more severe bone resorption, and greater postoperative calcium uptake into bones [8]. This is the classic scenario of hungry bone syndrome: after removal of the source of excess PTH, the previously high bone turnover leads to rapid remineralization, causing profound hypocalcemia [6]. The progressive increase in risk with each additional gram (OR 1.5 per gram, p=0.008 in a secondary analysis) supports a dose-response relationship.

Bilateral neck exploration was associated with a 3.5-fold increased risk, likely due to temporary ischemia or devascularization of normal parathyroid glands [9]. This finding supports the use of intraoperative PTH monitoring when available to limit unnecessary bilateral exploration [10]. In our center, bilateral exploration was reserved for complex cases (discordant imaging, multiglandular disease), but even so, the risk remained high. When combined with a large adenoma, the risk reached 45.5% (Table 3), suggesting an additive effect.

The percentage drop in PTH from preoperative to day 1 was the strongest independent predictor (OR = 5.0 for >80% drop). A cut-off of 75% drop gave an AUC of 0.81, indicating good discriminative ability. Early postoperative PTH measurement (on the morning of day 1) is a simple, inexpensive, and widely available tool. Patients with a >75% drop can be identified early and started on prophylactic calcium and calcitriol immediately, potentially preventing symptomatic hypocalcemia and reducing hospital stay. This approach has been validated in thyroid surgery [11] and is strongly supported by the present results.

Bone involvement (osteoporosis, bone pain, fractures, brown tumors) was strongly associated with hypocalcemia in univariate analysis but lost significance after adjusting for adenoma weight and PTH drop. This suggests that bone involvement is a marker of disease severity whose effect is mediated through large adenomas and marked PTH decline. Nevertheless, its presence should alert the surgeon to a higher risk of HBS.

Vitamin D deficiency was not an independent predictor in our final model, which contrasts with some previous reports [12]. This may be due to the high prevalence (71% of the cohort) and the overriding effect of adenoma weight and PTH kinetics. However, preoperative vitamin D repletion remains advisable to potentially reduce the severity of HBS.

Clinical implications and proposed risk stratification

Based on our findings, we propose a simple three-tier risk stratification (table 4).

Table 4. Risk stratification.

Risk level	Criteria	Prophylaxis
Low	No risk factor: adenoma ≤2 g, targeted surgery, PTH drop ≤75%	Routine monitoring only
Intermediate	Any one factor: adenoma >2 g OR bilateral exploration OR PTH drop >75%	Oral calcium 2 g/day + calcitriol 0.5 µg/day for 2 weeks
High	Two or three factors present	Aggressive: IV calcium if needed, calcitriol 1 µg/day, daily calcium monitoring for 3 days

Limitations

This study has several limitations. The retrospective, single-center design may introduce selection bias and limit generalizability. Intraoperative PTH monitoring was not available in this series, which could have refined the prediction of hypocalcemia. The composite definition of severe hypocalcemia, although more clinically relevant, still involves subjective elements (symptom reporting).

Nevertheless, the large sample size, the completeness of biological and bone data, and the rigorous penalized regression support the validity of the findings.

5. CONCLUSION

Severe postoperative hypocalcemia after parathyroidectomy for primary hyperparathyroidism – defined by a composite of biochemical, clinical, and therapeutic criteria – is independently predicted by adenoma weight >2 g, bilateral neck exploration, and a >75% drop in PTH by postoperative day 1. Early postoperative PTH measurement is a powerful, easy-to-use tool to identify at-risk patients and guide prophylactic calcium and calcitriol therapy. These factors should be incorporated into postoperative care protocols to reduce hospital stay and prevent complications.

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