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Impact of disease burden on early calcium dynamics after parathyroidectomy for primary hyperparathyroidism: An integrated model based on preoperative ultrasound and histopathological validation

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Abstract

Early postoperative hypocalcemia following parathyroidectomy for primary hyperparathyroidism remains difficult to predict using only preoperative parameters. This study aimed to evaluate whether a composite disease burden index combining preoperative biochemical severity with ultrasonography-derived adenoma volume and histopathological validation can predict early postoperative hypocalcemia. This retrospective cohort study included 83 patients who underwent parathyroidectomy for single-gland primary hyperparathyroidism. A composite disease burden index was calculated as the product of preoperative albumin-corrected calcium, parathyroid hormone, and ultrasonography-derived adenoma volume (available in 62 patients), with natural logarithmic transformation (log_CBIvol). Histopathological specimen dimensions were used to validate the ultrasonographic measurements. The primary outcome was early postoperative hypocalcemia requiring calcium and/or vitamin D supplementation. Early postoperative hypocalcemia occurred in 16 (19.3%) patients. The composite index was not associated with hypocalcemia in either univariable (odds ratio [OR] 0.61; $p = 0.324$) or multivariable analysis (OR 1.11; $p = 0.859$). Receiver operating characteristic analysis yielded an area under the curve (AUC) of 0.402 for log_CBIvol, indicating no discriminative ability of this parameter. Ultrasonographic and histopathological adenoma volumes showed a moderate correlation (Spearman's $\rho = 0.504$; $p < 0.001$). In contrast, the percentage decline in corrected calcium on postoperative day 1 demonstrated strong discriminative performance (AUC 0.827; sensitivity 87.5%, specificity 82.1% at a cutoff of -21.0%). Post-hoc power analysis confirmed that the study was underpowered for the primary variable (achieved power 5.9%), although clinically meaningful associations were detected for other parameters. Preoperative composite disease burden indices do not reliably predict early postoperative hypocalcemia. Early calcium dynamics are predominantly driven by dynamic metabolic adaptation rather than static preoperative disease burden, supporting a clinical focus on postoperative biochemical monitoring of patients.

Keywords: Hyperparathyroidism, primary; parathyroidectomy; hypocalcemia; calcium; parathyroid hormone; ultrasonography

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia resulting from inappropriate parathyroid hormone (PTH) secretion and is one of the most frequent causes of outpatient hypercalcemia in adults [1,2]. Parathyroidectomy remains the definitive and curative treatment for PHPT; however, disturbances in calcium homeostasis may persist or develop in the early postoperative period, despite technically successful surgery [1,3].

Early postoperative hypocalcemia is a clinically relevant issue, particularly in the context of ambulatory or short-stay surgery, as it may necessitate calcium and/or vitamin D supplementation and prolonged hospitalization [3,4]. Previous studies have demonstrated that postoperative calcium kinetics, rather than absolute calcium values, play a key role in identifying patients at risk for early hypocalcemia [4]. Nevertheless, the ability to reliably predict early postoperative hypocalcemia before surgery remains limited.

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Preoperative biochemical severity, particularly elevated calcium and PTH levels, has been widely investigated as a potential predictor of postoperative calcium disturbance [3,5]. Although higher biochemical values have been associated with greater postoperative calcium decline, biochemical parameters alone have shown inconsistent performance in predicting clinically significant hypocalcemia [3,6]. This suggests that biochemical severity may not fully reflect the underlying disease burden that influences postoperative calcium dynamics.

Accordingly, structural disease burden, most commonly represented by parathyroid adenoma size or volume, has been proposed as an additional determinant of postoperative outcomes [5,6]. Several studies have explored the relationship between adenoma volume and perioperative biochemical changes, reporting variable and sometimes conflicting results [6]. Furthermore, the accuracy of preoperative ultrasonography in reflecting the true histopathological tissue burden has not been fully elucidated, despite its widespread use in surgical planning [7]. Tarım et al. reported a significant correlation between intraoperative PTH levels and adenoma volume and weight in patients with single adenoma PHPT, emphasizing the potential role of volumetric parameters in surgical decision-making [8].

Therefore, the present study aimed to evaluate whether an integrated disease burden model combining preoperative biochemical severity with ultrasonography-derived structural measurements and histopathological validation is associated with early postoperative calcium dynamics and clinically significant hypocalcemia following following parathyroidectomy for PHPT.

Material and Methods

Study Design and Patient Selection

This study was designed as a retrospective, single center, observational cohort study. Patients aged ≥ 18 years who underwent elective parathyroidectomy for PHPT between January 1, 2016, and December 31, 2025, at Bolu Abant İzzet Baysal University Faculty of Medicine Hospital were evaluated. This retrospective study was approved by the Ethics Committee of Bolu Abant İzzet Baysal University Faculty of Medicine (Approval Number and Date: 2026/36 and 03/02/2026).

During the study period, 125 patients underwent parathyroidectomy. Patients were excluded if they had multiglandular parathyroid disease, underwent concomitant thyroid surgery, had secondary or tertiary hyperparathyroidism, had a history or diagnosis of malignancy affecting calcium or bone metabolism, had multiple endocrine neoplasia multiple endocrine neoplasia syndrome, or had chronic kidney disease. Patients with unsuccessful surgery, defined as persistent or recurrent disease within the first three postoperative months based on biochemical, radiological, and pathological evaluations were also excluded. After applying the exclusion criteria, only patients with single-gland PHPT and complete clinical, biochemical, ultrasonographic, operative, and pathological data were included in the final analysis (Figure 1).

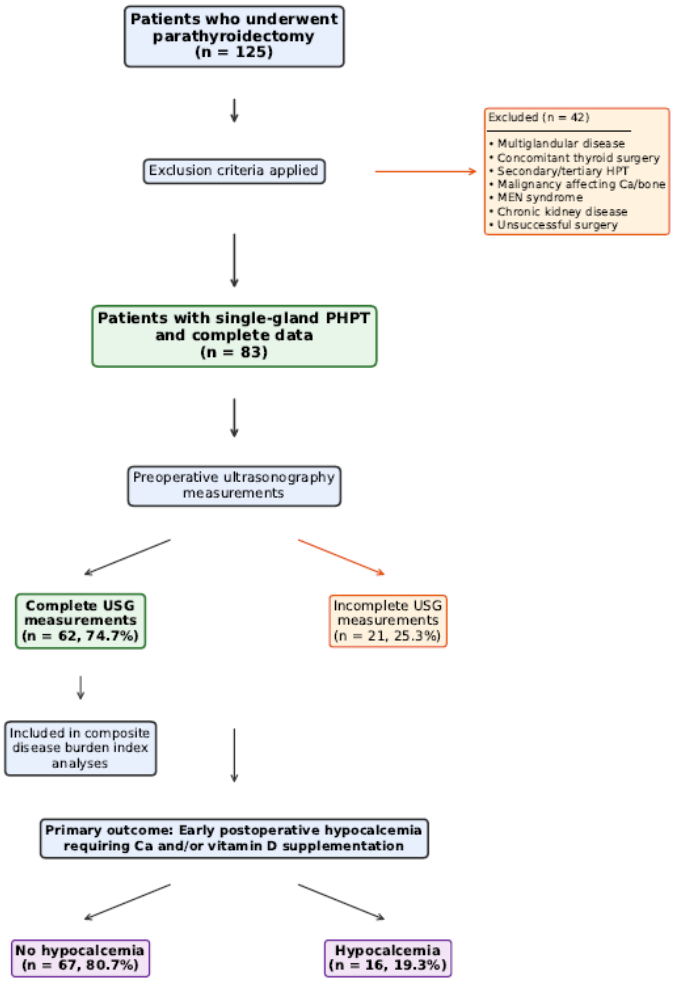

Figure 1. Flow diagram of patient selection and exclusion criteria.

Demographic characteristics (age and sex), preoperative laboratory parameters, radiological findings, intraoperative variables and pathological results were obtained retrospectively from the hospital electronic medical record system and the institutional Picture Archiving and Communication System.

Assessment of Disease Burden

Preoperative disease burden was evaluated using biochemical severity and structural parameters.

The biochemical parameters included preoperative serum PTH, albumin-corrected calcium, phosphorus, magnesium, chloride, 25-hydroxyvitamin D, alkaline phosphatase, and estimated glomerular filtration rate (eGFR). All laboratory values were obtained within 30 days prior to surgery.

The structural disease burden was assessed using preoperative neck ultrasonography. Three orthogonal dimensions of the parathyroid lesion (x, y, and z) were recorded, and the lesion volume was calculated using the prolate ellipsoid formula ($\pi/6 \times x \times y \times z$). The maximum lesion diameter (d_max) was also recorded. Histopathological specimen dimensions were documented, and the pathological adenoma volume

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was calculated using the same ellipsoid formula to validate ultrasonographic measurements.

To quantify the disease burden as a single continuous parameter reflecting both biochemical severity and structural tumor load, a composite disease burden index was calculated as the arithmetic product of preoperative albumin-corrected calcium (mg/dL), preoperative PTH (pg/mL), and ultrasonography-derived adenoma volume (mm^3). A diameter-based variant using the maximum adenoma diameter (mm) instead of the volume was also calculated. Given the highly skewed distribution of these composite indices, natural logarithmic transformation was applied prior to statistical analysis (log_CBIvol and log_CBIdmax, respectively).

Postoperative Biochemical Assessment and Outcomes

Postoperative biochemical evaluation included serum PTH, albumin, and corrected calcium levels measured on postoperative day 1. Absolute and percentage changes in calcium and PTH levels (delta and percent delta values) were calculated to assess early postoperative biochemical dynamics.

The primary outcome was early postoperative hypocalcemia, defined as the requirement for calcium and/or active vitamin D supplementation initiated on postoperative day 1 based on a serum albumin-corrected calcium level below 8.2 mg/dL (institutional laboratory reference range: 8.2 – 10.2 mg/dL) and/or the presence of clinical symptoms attributable to hypocalcemia (perioral or acral paresthesia, carpopedal spasm, positive Chvostek or Trousseau sign). Supplementation decisions were made at the discretion of the treating surgeon based on biochemical and clinical criteria. All patients who developed clinical hypocalcemic symptoms also met the criteria for supplementation therapy, and the two classifications were consistent.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 27.0; IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation or median with interquartile range (Q1-Q3), depending on the data distribution. Categorical variables are expressed as frequencies and percentages.

The normality of continuous variables was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. The correlation between ultrasonography-derived and histopathological adenoma dimensions was assessed using Spearman's rank correlation coefficients.

Univariable logistic regression analyses were performed to evaluate the associations between candidate predictors and early postoperative hypocalcemia. Variables with clinical relevance or univariable significance were considered for multivariable modeling. Given the limited number of outcome events (n = 16 in the full cohort; n = 10 in the ultrasonography subgroup), the model complexity was constrained by the events-per-variable principle. A sensitivity analysis incorporating preoperative 25-hydroxyvitamin D levels was performed to assess potential confounding factors. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

The discriminative performance of the disease burden parameters and postoperative calcium dynamics was evaluated using receiver operating characteristic (ROC) curve analysis. Optimal cutoff values were determined using the Youden index, and the corresponding sensitivity and specificity values were calculated. Statistical significance was set at $p < 0.05$.

A post-hoc power analysis for the primary study variable (log_CBIvol) was performed using G*Power software (version 3.1.9.7) based on the observed odds ratio, event rate, and sample size in the ultrasonography subgroup.

Methodological Limitations

The retrospective and single-center design of this study may limit its generalizability. The exclusion of patients with multiglandular disease and concomitant thyroid surgery was necessary to reduce confounding factors but may restrict the applicability of the findings to broader PHPT populations. Additionally, ultrasonography-based measurements are subject to operator-dependent variability. Histopathological adenoma weight was not routinely reported in pathology specimens during the study period; therefore, pathological validation was based on specimen dimensions and calculated volume rather than weight.

Results

Study Population

A total of 83 patients who underwent parathyroidectomy for PHPT during the study period met the inclusion criteria for this study. Among these, 62 patients (74.7%) had complete preoperative ultrasonography measurements, enabling the calculation of composite disease burden indices, and were included in the ultrasonography-based analyses. Early postoperative hypocalcemia requiring calcium and/or vitamin D supplementation was observed in 16 patients (19.3%).

Baseline Characteristics and Preoperative Findings

The baseline demographic and preoperative biochemical characteristics stratified by postoperative hypocalcemia status are shown in Table 1. Age and sex distributions were comparable between patients with and without postoperative hypocalcemia, although all 16 patients who developed hypocalcemia were women ($p = 0.064$).

Patients who developed postoperative hypocalcemia had significantly lower preoperative corrected calcium levels than those who did not (median 10.7 vs. 11.2 mg/dL; p =

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0.017). Preoperative PTH levels tended to be lower in the hypocalcemia group; however, this difference did not reach statistical significance (median 168.6 vs. 276.1 pg/mL; p = 0.066). The eGFR was significantly higher in the hypocalcemia group (median 103.7 vs. 94.9 mL/min/1.73 m²; p = 0.014). No significant intergroup differences were observed in terms of alkaline phosphatase, 25-hydroxyvitamin D, or magnesium levels or ultrasonography-derived parathyroid volume.

The composite disease burden index based on ultrasonography-derived volume (log_CBIvol) did not differ significantly between patients without and with postoperative hypocalcemia (6.21 ± 0.78 vs. 5.95 ± 0.72; p = 0.328).

Table 1. Baseline demographic and preoperative characteristics according to early postoperative hypocalcemia

Variable	No hypocalcemia (n = 67)	Hypocalcemia (n = 16)	p value
Age, years	56.0 (47.0 – 62.5)	53.0 (49.8 – 57.0)	0.124
Female sex, n (%)	54 (80.6)	16 (100)	0.064†
Preoperative PTH, pg/mL	276.1 (183.1 – 396.6)	168.6 (143.4 – 301.9)	0.066
Preoperative corrected Ca, mg/dL	11.2 (10.5 – 11.5)	10.7 (10.2 – 11.1)	**0.017**
ALP, U/L‡	108.5 (76.5 – 140.8)	110.0 (82.0 – 134.0)	0.827
25(OH) vitamin D, ng/mL‡	16.0 (9.4 – 20.3)	14.0 (11.2 – 16.2)	0.618
Magnesium, mg/dL‡	1.9 (1.8 – 2.0)	1.9 (1.7 – 2.1)	0.918
eGFR, mL/min/1.73 m²	94.9 (79.2 – 103.0)	103.7 (98.2 – 108.4)	**0.014**
USG-derived adenoma volume, mm³§	570.5 (175.9 – 1095.6)	420.4 (170.4 – 648.0)	0.334
log_CBIvol§	6.21 ± 0.78	5.95 ± 0.72	0.328

Data are presented as median (Q1-Q3) or mean ± standard deviation, as appropriate. Bold p-values indicate statistical significance (p < 0.05). † Fisher's exact test. ‡ Available for ALP (n = 73), 25(OH) Vitamin D (n = 63), and magnesium (n = 64). § Available in 62 patients with complete ultrasonographic measurements (no hypocalcemia, n = 52; hypocalcemia, n = 10). Abbreviations: ALP, alkaline phosphatase; Ca, calcium; eGFR, estimated glomerular filtration rate; log_CBIvol, natural logarithm of the composite disease burden index calculated using ultrasonography-derived adenoma volume; PTH, parathyroid hormone; USG, ultrasonography.

Ultrasonographic and Histopathological Validation

Histopathological specimen dimensions were available for all 83 patients. In the 62 patients with complete ultrasonographic data, a moderate and statistically significant correlation was observed between ultrasonography-derived and histopathological adenoma volumes (Spearman's ρ = 0.504; p < 0.001). The maximum ultrasonographic and histopathological diameters also showed a significant correlation (Spearman's ρ = 0.486; p < 0.001). The corresponding Pearson correlation coefficients were 0.821 for volume and 0.518 for the maximum diameter (Table 2). The discrepancy between the parametric and nonparametric volume estimates reflects the influence of outlying values in the upper volumetric range.

Table 2. Correlation between ultrasonographic and histopathological adenoma measurements (n = 62)

Parameter pair	Spearman ρ	p value	Pearson r	p value
USG volume - Pathological volume	0.504	< 0.001	0.821	< 0.001
USG d_max - Pathological d_max	0.486	< 0.001	0.518	< 0.001

The discrepancy between the Pearson and Spearman coefficients for volume reflects the influence of extreme volumetric values on parametric estimates. Abbreviations: d_max, maximum diameter; USG, ultrasonography.

Early Postoperative Biochemical Response

The early postoperative biochemical changes are summarized in Table 3. The magnitude of the absolute calcium decline was significantly greater in patients who developed postoperative hypocalcemia (median -2.56 vs. -1.84 mg/dL; p < 0.001). The percentage change in corrected calcium levels was markedly higher in the hypocalcemia group than in patients without hypocalcemia (-24.3 ± 4.0% vs. -16.4 ± 8.2%; p < 0.001), with a large effect size.

Although substantial postoperative reductions in PTH levels were observed in both groups, the absolute changes in PTH levels were not significantly associated with clinical hypocalcemia (p = 0.126).

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Table 3. Early postoperative biochemical changes according to hypocalcemia status.

Variable	No hypocalcemia (n = 67)	Hypocalcemia (n = 16)	p value
Δ corrected Ca, mg/dL	-1.84 (-2.26 to -1.22)	-2.56 (-2.82 to -2.34)	**< 0.001**
%Δ corrected Ca	-16.4 ± 8.2	-24.3 ± 4.0	**< 0.001**
Δ PTH, pg/mL	-254.3 (-379.9 to -131.6)	-144.4 (-272.2 to -105.0)	0.126

Data are presented as median (Q1-Q3) or mean ± standard deviation, as appropriate. Bold p-values indicate statistical significance ($p < 0.05$). Abbreviations: PTH, parathyroid hormone; Δ, absolute change between preoperative and postoperative day 1 measurements; %Δ, percentage change.

Disease Burden Index and Prediction of Hypocalcemia

The results of the univariable and multivariable logistic regression analyses are presented in Table 4. In the univariable analysis, the composite disease burden index (log_CBIvol) was not associated with early postoperative hypocalcemia (odds ratio [OR] 0.61, 95% confidence interval [CI] 0.23 – 1.62; p = 0.324). Preoperative corrected calcium showed a significant univariable association (OR 0.39, 95% CI 0.16 – 0.92; p = 0.032). Preoperative eGFR was also significantly associated with hypocalcemia in the univariable analysis (OR 1.05, 95% CI 1.01 – 1.09; p = 0.028). Preoperative 25-hydroxyvitamin D (OR 0.96, 95% CI 0.87 – 1.05; p = 0.390) and magnesium (OR 0.99, 95% CI 0.08 – 12.98; p = 0.996) levels were not significantly associated with postoperative hypocalcemia.

In the primary multivariable model adjusted for preoperative corrected calcium, log_CBIvol remained non-significant (OR 1.11, 95% CI 0.35 – 3.53; p = 0.859), whereas preoperative corrected calcium retained its independent association (OR 0.26, 95% CI 0.08 – 0.90; p = 0.033). Model calibration was acceptable (Hosmer-Lemeshow p = 0.133).

A sensitivity analysis including preoperative 25-hydroxyvitamin D alongside log_CBIvol and corrected calcium (n = 46; 6 events) showed no substantial change in the direction or significance of estimates; however, statistical power was severely limited due to the reduced sample size and events-per-variable ratio of 2.0, precluding a reliable interpretation (Table 4).

Table 4. Logistic regression analysis of early postoperative hypocalcemia

Panel A: Univariable analyses			
Variable	**n**	**OR (95% CI)**	**p value**
log_CBIvol	62	0.61 (0.23 – 1.62)	0.324
Preoperative corrected Ca, mg/dL	83	0.39 (0.16 – 0.92)	**0.032**
Preoperative eGFR, mL/min/1.73 m²	83	1.05 (1.01 – 1.09)	**0.028**
25(OH) Vitamin D, ng/mL	63	0.96 (0.87 – 1.05)	0.390
Magnesium, mg/dL	64	0.99 (0.08 – 12.98)	0.996
Panel B: Primary multivariable model (n = 62; 10 events)			
Variable		**OR (95% CI)**	**p value**
log_CBIvol		1.11 (0.35 – 3.53)	0.859
Preoperative corrected Ca, mg/dL		0.26 (0.08 – 0.90)	**0.033**
Hosmer-Lemeshow goodness of fit: $\chi^2 = 12.429$, p = 0.133.			
Panel C: Sensitivity analysis (n = 46; 6 events; events-per-variable ratio = 2.0)			
Variable		**OR (95% CI)**	**p value**
log_CBIvol		1.51 (0.27 – 8.43)	0.637
Preoperative corrected Ca, mg/dL		0.29 (0.05 – 1.74)	0.174
25(OH) Vitamin D, ng/mL		0.96 (0.85 – 1.08)	0.481

Hosmer-Lemeshow goodness of fit: $\chi^2 = 5.449$, p = 0.605. The results should be interpreted with caution, given the low events per variable ratio. Abbreviations: Ca, calcium; CI, confidence interval; eGFR, estimated glomerular filtration rate; log_CBIvol, natural logarithm of the composite disease burden index calculated using ultrasonography-derived adenoma volume; OR, odds ratio.

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Receiver Operating Characteristic Analysis

ROC curve analysis was performed for log_CBIvol, preoperative corrected calcium, and percentage of calcium change on postoperative day 1 (Table 5; Figure 2). The composite disease burden index demonstrated no discriminative ability to predict early postoperative hypocalcemia (area under the curve [AUC] = 0.402). As this value fell below the reference line, no clinically applicable cutoff was identified.

Table 5. Receiver operating characteristic analysis for the prediction of early postoperative hypocalcemia

Variable	AUC	Youden cutoff	Sensitivity (%)	Specificity (%)
log_CBIvol	0.402	-	-	-
Preoperative corrected Ca, mg/dL	0.770	≤ 11.14	87.5	50.7
%Δ corrected Ca	0.827	≤ -21.0%	87.5	82.1

For log_CBIvol, the AUC fell below the reference line (0.50), indicating no discriminative ability; therefore, the cutoff values could not be determined. Abbreviations: AUC, area under the receiver operating characteristic curve; log_CBIvol, natural logarithm of the composite disease burden index; %Δ, percentage change in corrected calcium between preoperative and postoperative day 1 measurements.

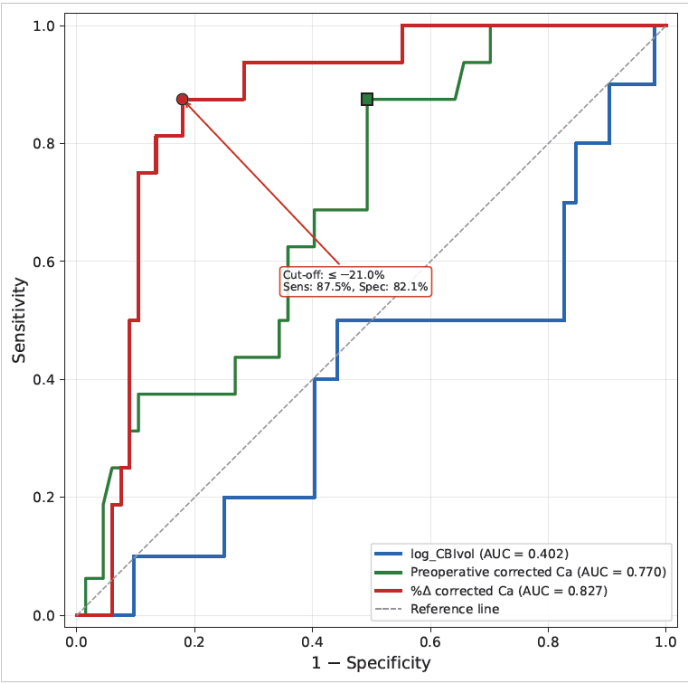

Figure 2. Receiver operating characteristic curves for log_CBIvol, preoperative corrected calcium, and percentage calcium change on postoperative day 1 for predicting early postoperative hypocalcemia.

Preoperative corrected calcium levels showed moderate discriminative ability (AUC 0.770). Using the Youden index, the optimal cutoff was ≤ 11.14 mg/dL, yielding a sensitivity of 87.5% and a specificity of 50.7%.

In contrast, the percentage decline in corrected calcium on postoperative day 1 demonstrated the strongest discriminative performance (AUC = 0.827). The Youden-derived optimal cutoff of ≤ -21.0% provided a sensitivity and specificity of 87.5% and 82.1%, respectively.

Post-hoc Power Analysis

Post-hoc power analysis for the primary study variable (log_CBIvol) using the observed OR of 0.61, an event rate of 16.1%, a sample size of 62, and a two-sided alpha of 0.05 yielded a power of 5.9%. This confirms that the study was substantially underpowered to detect a statistically significant association of this magnitude with the composite disease burden index. However, within the same cohort, preoperative corrected calcium levels were significantly associated with postoperative hypocalcemia (p = 0.032), indicating that the sample size was sufficient to identify clinically meaningful associations when the underlying effect size was adequate.

Discussion

The present study demonstrated that a composite disease burden index incorporating preoperative biochemical severity and ultrasonographic adenoma volume does not predict early postoperative hypocalcemia following parathyroidectomy for PHPT. The composite index showed no discriminative ability (AUC 0.402), and neither adenoma volume nor the composite metric was associated with the need for supplementation in logistic regression analyses. In contrast, the percentage decline in corrected calcium on postoperative day 1 emerged as the strongest predictor (AUC 0.827; sensitivity 87.5%, specificity 82.1% at a cutoff of -21.0%), reinforcing the primacy of dynamic metabolic response over static anatomical parameters. Preoperative corrected calcium was the only static variable with an independent predictive value (OR 0.26, p = 0.033), while an unexpected paradoxical pattern was observed: patients who developed hypocalcemia had lower preoperative calcium and PTH levels.

These findings should be considered in the context of previous studies demonstrating that early calcium dynamics are highly variable and not fully explained by preoperative biochemical severity alone [1-4]. This uncertainty has led to growing interest in disease burden-based models that incorporate anatomical, biochemical, and kinetic parameters [5-9]. In the present study, we specifically investigated whether static preoperative disease burden, quantified by a composite index incorporating biochemical severity and ultrasonographic adenoma volume

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and validated by histopathological measurements, could predict early postoperative calcium behavior and the need for calcium supplementation. Despite the presumed association between disease burden components and preoperative biochemical severity, our findings demonstrate that the composite index did not predict early hypocalcemia or the need for supplementation. These results challenge the assumption that larger adenomas necessarily confer a higher risk of early postoperative calcium derangement.

Unlike Kaderli et al. [10], who focused on dynamic postoperative metabolic trajectories, and Minisola et al. [11], who provided a comprehensive epidemiological framework, our study specifically tested whether preoperative static disease burden, combining biochemical severity with ultrasonographically measured adenoma volume in a single composite metric, could serve as a preoperative-risk stratification tool. Our negative findings complement, rather than duplicate, existing dynamic models by empirically demonstrating the limited predictive value of static approaches.

Several studies have reported correlations between adenoma size and preoperative calcium or PTH levels, suggesting that anatomical burden reflects disease severity [5,10,12]. Tarım et al. similarly demonstrated that intraoperative PTH levels correlated with adenoma volume and weight in patients with single-adenoma PHPT [8]. However, consistent with our findings, more recent evidence indicates that this relationship does not translate into reliable postoperative risk stratification [13,14]. Our data reinforce the notion that preoperative structural metrics alone are insufficient to capture the complexity of postoperative calcium homeostasis.

Ultrasonographic-histopathological validation analysis showed a moderate but significant correlation (Spearman's $\rho = 0.504$ for volume and 0.486 for maximum diameter). Although this confirms that ultrasonography provides a reasonable estimate of true adenoma size, the imperfect correlation suggests that measurement variability in the preoperative assessment may further attenuate the predictive value of volume-based indices.

The key explanation for these negative findings lies in the dynamic nature of calcium regulation after surgery. Early hypocalcemia after parathyroidectomy is not a static consequence of tissue removal but rather the result of a rapid physiological transition characterized by abrupt PTH withdrawal, skeletal calcium uptake, and individual differences in bone remineralization capacity [10,11]. This dynamic response, often referred to in the context of hungry bone physiology, cannot be adequately predicted using preoperative imaging parameters alone [15].

An unexpected but noteworthy finding was the direction of the preoperative biochemical differences between groups. Patients who developed hypocalcemia had lower preoperative corrected calcium and PTH levels than those who did not develop hypocalcemia. This paradoxical pattern suggests that the risk of hypocalcemia in patients with PHPT may not follow a simple severity gradient. One possible explanation is that patients with lower preoperative calcium levels are closer to the threshold for symptomatic hypocalcemia, such that even a modest postoperative decline triggers clinical symptoms. Additionally, the significantly higher eGFR in the hypocalcemia group may reflect more efficient renal calcium excretion, contributing to a steeper decline in postoperative calcium levels.

Importantly, our results showed that the percentage of calcium decline on postoperative day 1 was the strongest predictor of supplementation need (AUC 0.827; sensitivity 87.5%, specificity 82.1% at a cutoff of -21.0%). This finding aligns with studies emphasizing early postoperative calcium kinetics as a more meaningful clinical indicator than preoperative adenoma characteristics [16-18]. In this context, our study does not represent a failure of predictive modeling but rather a validation of a biologically grounded concept: dynamic metabolic response outperforms static anatomical burden in predicting clinical outcomes.

These observations have direct clinical implications. Reliance on adenoma size or ultrasonographic volume to guide postoperative calcium management may be misleading. Instead, close monitoring of early calcium trajectories, particularly a corrected calcium decline exceeding 21% within the first postoperative day, and individualized supplementation strategies based on dynamic biochemical responses appear to be more physiologically sound and clinically effective.

The principal limitations of this study include its retrospective single-center design, the relatively small sample size with limited statistical power for the primary composite index (achieved power 5.9%), and the absence of specific bone turnover markers beyond alkaline phosphatase. Histopathological adenoma weight was not routinely documented, limiting the validation of volume-based comparisons. The finding that preoperative corrected calcium demonstrated a statistically significant association ($p = 0.032$) within the same cohort suggests that the sample size was capable of detecting clinically meaningful associations; however, the possibility that a larger study might detect a weaker but real association for the composite index cannot be excluded. Future prospective studies with larger sample sizes and serial postoperative calcium measurements may further clarify the interplay between preoperative disease burden and postoperative metabolic adaptation.

Conclusion

Preoperative composite disease burden indices incorporating biochemical severity and ultrasonographic adenoma volume do not reliably predict early postoperative hypocalcemia after parathyroidectomy for PHPT. Although ultrasonographic measurements show a moderate correlation with histopathological dimensions, the static nature of these parameters fails to capture the dynamic metabolic adaptation that drives early calcium disturbance. The percentage decline in corrected calcium on postoperative day 1 (AUC 0.827) emerged as the most effective discriminator, supporting a clinical focus on early biochemical monitoring rather than preoperative structural risk stratification.

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Ethical Approval
This retrospective study was approved by the Ethics Committee of Bolu Abant İzzet Baysal University Faculty of Medicine (approval number and date: 2026/36 – 03/02/2026).

Patient Consent
Owing to the retrospective design of the study, the requirement for informed consent was waived by the Ethics Committee of Bolu Abant İzzet Baysal University Faculty of Medicine

Conflict of Interest
The authors confirm the absence of any conflicts associated with this work.

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