ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

ORIGINAL ARTICLE
Endocrinol Res Pract. 2026;30(4):267-276

The Evaluation of the Predictive Value of Early Postoperative Biochemical Parameters for Remission in Patients with Acromegaly

ABSTRACT

Objective: This study aimed to evaluate the predictive value of growth hormone (GH), insulin-like growth factor-1 (IGF-1), calcium (Ca), and phosphorus (P) levels in the first 2-4 days after surgery for achieving biochemical remission in patients with newly diagnosed acromegaly.

Methods: This retrospective cohort study included patients with acromegaly who underwent surgery. Preoperative and early postoperative days 2-4 (POD_{2-4}), 3rd month, and 12th month serum levels of GH, IGF-1, Ca, and P were obtained. Age-normalized IGF-1 levels defined remission at 3-6 months, and patients were grouped accordingly.

Results: Biochemical remission was achieved in 44 of 68 patients (64.7%). Preoperative GH, IGF-1, and Ca were significantly higher in the non-remission group (all $P < .05$), while P did not differ. In POD_{2-4}, all parameters, including P, were significantly higher in the non-remission group ($P < .05$). Receiver operating characteristic (ROC) analysis showed that a GH ≤1.28 in POD_{2-4} (AUC = 0.858, sensitivity: 0.74, specificity: 0.88) and a ≥45.29% decrease in IGF-1 from preoperative values (AUC = 0.816; sensitivity: 0.73, specificity: 0.79) predicted remission. At 12 months, GH and IGF-1 remained significantly different, whereas Ca and P did not ($P = .67$ and $P = .20$).

Conclusion: In patients with acromegaly, GH, IGF-1, Ca, and P levels measured in the first 2-4 days after surgery were found to be significantly lower in the remission group than in those who did not achieve remission. Postoperative GH levels and the percentage decrease in IGF-1 levels were associated with remission and may help with early risk stratification.

Keywords: Acromegaly, biochemical remission, calcium, growth hormone, insulin-like growth factor-1, phosphorus, surgical remission

Introduction

Acromegaly is a rare disorder characterized by chronic hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), most commonly caused by a pituitary adenoma, and it affects multiple organs and systems. The incidence of acromegaly ranges from 0.2 to 1.1 per 100 000 individuals per year.[1] Chronic exposure to elevated GH and IGF-1 levels also leads to overgrowth of epithelial and visceral tissues, increasing the risk of cardiovascular disease, hyperglycemia, certain malignancies, hypertrophic arthropathy, obstructive sleep apnea, and other metabolic disorders.[2–5]

In this lifelong disease with comorbidities, biochemical remission and clinical evaluation of disease activity are important for follow-up. Therefore, early prediction of postoperative remission and the identification of the most appropriate parameter remain of interest. Preoperative parameters such as higher preoperative GH levels, male gender, cavernous sinus invasion, and larger tumor size have been associated with lower early remission rates.[6,7] Although postoperative GH (particularly on days 1-14) may provide useful information for the early assessment of biochemical remission, it is not a definitive criterion for early remission.[8] In contrast, the predictive value of IGF-1 remains controversial because of its longer half-life, with conflicting evidence regarding its ability to predict remission.[9,10]

Studies have shown that phosphorus (P) and calcium (Ca) homeostasis are also altered in patients with acromegaly.[2,11] These changes are thought to reflect the effects of GH and IGF-1 on bone mineral metabolism, characterized by increased osteoclastic and osteoblastic activity.[12,13] Growth hormone and IGF-1 stimulate osteoclastic bone resorption, increasing Ca release into the circulation. Mild hyperphosphatemia, commonly observed in acromegaly,

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Received: April 12, 2026
Revision Requested: May 12, 2026
Last Revision Received: July 5, 2026
Accepted: August 7, 2026
Publication Date: September 1, 2026

Cite this article as: Babayeva A, Coskun M, Ozturk O, *et al*. The evaluation of the predictive value of early postoperative biochemical parameters for remission in patients with acromegaly. *Endocrinol Res Pract.* 2026;30(4):267-276.

DOI: 10.5152/erp.2026.26985

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results from increased intestinal phosphate absorption and renal phosphate reabsorption mediated by GH and IGF-1.[14,15] Additionally, high GH levels also increase intestinal calcium absorption through vitamin D-mediated mechanisms.[16,17] Changes in Ca and P levels before and after treatment, as well as their relationship with remission, have been demonstrated in patients with acromegaly.[2,12,15] Considering these findings together, Ca and P may provide useful information on disease activity in acromegaly. Although serum P levels are known to be elevated during the active disease, there is still no consensus regarding their clinical significance or their role in postoperative follow-up.[2,15,18]

Surgical treatment for acromegaly is considered the first-line approach according to current guidelines. However, biochemical remission is not achieved in all patients. Therefore, identifying reliable biomarkers to predict remission is increasingly critical for personalizing patient management. Identifying patients with a low likelihood of early remission, particularly after surgery, enables optimization of treatment strategies. As emphasized in recent years by international guidelines, initiating medical therapy, including somatostatin analogs, either primarily or early, is increasingly being considered in cases where surgical success is anticipated to be low.[3,19] While previous studies have investigated the role of postoperative GH and IGF-1 levels in predicting remission, few studies have specifically focused on IGF-1 measurements and changes in the first postoperative days. Furthermore, there is insufficient data in the literature demonstrating changes in Ca and P levels in the early postoperative period.

In this context, this study aimed to evaluate GH, IGF-1, and serum Ca and P levels as potential biomarkers of disease activity during the first 2-4 days after surgery for achieving biochemical remission in patients with newly diagnosed acromegaly. It also aimed to demonstrate the course of these biochemical parameters during the first year of follow-up.

Material and Methods

Study Design

In this retrospective cohort study, the authors analyzed data from patients with acromegaly who were treated at a tertiary care endocrinology clinic. The study included newly diagnosed patients who underwent transsphenoidal surgery at the center between 2018 and 2024, with no prior surgery, radiotherapy, or medical treatment for acromegaly. The same surgical team performed all procedures. Data were obtained from departmental archives and the hospital electronic medical records. Acromegaly was diagnosed based on clinical features, elevated age- and gender-adjusted IGF-1 levels, and GH >1 mcg/dL during an oral glucose tolerance test (OGTT).[8,20] Patients with chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2), chronic liver disease, uncontrolled thyroid dysfunction during the perioperative period, acute kidney injury, or conditions or medications affecting Ca–P metabolism (e.g., calcium or vitamin D supplementation, thiazide diuretics, bisphosphonates, denosumab, and phosphate-binding agents) were excluded. Patients receiving levothyroxine replacement therapy were included if euthyroidism was maintained during the perioperative period. Patients with persistent disease who underwent reoperation during the first postoperative year were also excluded. The study was approved by Gazi University Ethics Committee (E-77082166-604.01-1174274, February 19, 2025). Due to the retrospective design of the study, informed consent was not obtained from the included patients.

Age at diagnosis, gender, and history of diabetes and hypertension were recorded. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Adenoma size was defined as the largest diameter on magnetic resonance imaging (MRI). Preoperative measurements of GH, IGF-1, basal cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), free thyroxine (fT4), prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), Ca, P, 25-OH vitamin D, and creatinine were recorded. The ratio of IGF-1 to the age- and gender-adjusted upper limit of normal (ULN) was expressed as IGF-1 ULN. Calcium levels were reported based on the formula: albumin-corrected Ca (corrected Ca = serum Ca + 0.8 × (4 – patient's albumin)). Growth hormone, IGF-1, Ca, and P levels were measured from fasting morning blood measurements obtained during the early postoperative days. Although most measurements were performed on postoperative day 3 (POD_3), values obtained between $POD_{2\text{-}4}$ were also available. Therefore, this time period was used as the $POD_{2\text{-}4}$ in this article. The percentage decrease in IGF-1, Ca, and P at $POD_{2\text{-}4}$ relative to preoperative values was calculated as ([preoperative value – $POD_{2\text{-}4}$ value] / preoperative value) × 100.

Growth hormone, IGF-1, IGF-1 ULN, Ca, and P results were recorded from measurements taken 3 and 12 months after surgery in all patients. Biochemical remission was assessed in all patients at the 3-month follow-up. According to current consensus recommendations, normal IGF-1 levels (IGF-1 ULN ≤1) were considered biochemical remission.[8,20] Additionally, a random GH level <1 ng/mL was consistent with remission criteria.[21] In patients with discordance between GH and IGF-1 results or borderline biochemical findings at the 3-month assessment, remission status was clarified through repeated biochemical evaluations or an OGTT, with a nadir GH <0.4 ng/mL, during the 3-6 month follow-up. Patients were classified as in remission or not in remission according to these criteria. Those who did not achieve remission within 3-6 months received medical therapy; all 3-month values were obtained before treatment initiation.

Hormone and Biochemical Assays

Serum GH and IGF-1 levels were measured by electrochemiluminescence immunoassay. Thyroid-stimulating hormone, fT4, ACTH, cortisol, FSH, LH, and 25(OH) vitamin D were analyzed using a chemiluminescent immunoassay, whereas serum Ca and inorganic P were measured by routine colorimetric methods.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± SD for normally distributed

MAIN POINTS

- Biochemical parameters in the early postoperative days may contribute to predicting remission in newly diagnosed patients with acromegaly.
- Growth hormone levels and the percentage decrease in insulin-like growth factor-1 measured on postoperative days 2-4 were associated with remission and may be helpful for early risk stratification after pituitary surgery.
- Postoperative calcium and phosphorus levels differed between patients who achieved remission and those who did not; however, the clinical implications of these findings require further investigation.

data or median (interquartile range) for non-normally distributed data. Normality of distribution was assessed using the Shapiro–Wilk test. Group comparisons were performed using the chi-square test for categorical variables, the independent *t*-test for normally distributed continuous variables, and the Mann–Whitney *U*-test for non-normally distributed variables. Correlations were analyzed with Spearman's correlation coefficient. Longitudinal changes in normally distributed variables (Ca and P) were analyzed using repeated-measures of analysis of variance (ANOVA). Growth hormone, IGF-1, and IGF-1 ULN, which were not normally distributed, were analyzed using the Friedman test with Bonferroni-adjusted post hoc pairwise comparisons. Group-specific temporal patterns (remission and non-remission) were visualized using separate longitudinal line plots for each parameter. Receiver operating characteristic (ROC) analysis was performed to calculate the area under the curve (AUC) and determine the optimal cutoff values for absolute GH levels and percentage decrease in IGF-1, Ca, and P to predict biochemical remission. Optimal cutoff values were identified using the maximum Youden index (sensitivity + specificity − 1), which represents the best balance between sensitivity (true positive rate) and specificity (true negative rate). To evaluate the independent predictive value of early postoperative biochemical markers, 2 multivariable logistic regression models were constructed, including age at diagnosis, adenoma size, and granulation pattern as covariates. $POD_{2\text{-}4}$ GH and the percentage decrease in IGF-1 were analyzed separately due to the limited sample size and potential collinearity. All statistical analyses and visualizations were performed using R (R Core Team, 2023) and the RStudio IDE (Posit Team, 2023) and IBM Statistical Package for the Social Sciences Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics

Sixty-eight patients with newly diagnosed acromegaly were included in the study. General characteristics of the participants are shown in Table 1. Biochemical remission was achieved in 44 patients. In 12 patients with borderline IGF-1 levels or discordant GH–IGF-1 findings, remission status was confirmed by repeated hormone measurements and/or OGTT performed 3-6 months after surgery. The mean age at diagnosis was 43.80 ± 11.82 years and was significantly lower in postoperative non-remission patients (39.70 ± 11.10 years) ($P = .03$). There were no significant differences between the 2 groups in gender, BMI, or the presence of diabetes and hypertension (all $P > .05$). The majority of patients had macroadenomas (n = 59), and the median adenoma size was 14.0 mm (11.75-24.25). There was a statistically significant difference in adenoma size between the groups ($P = .03$). Based on adenoma size, biochemical remission was achieved in all patients with microadenomas (9/9, 100%), in 34 of 54 patients with macroadenomas (63.0%), and in 1 of 5 patients with giant adenomas (20.0%). Histopathological granulation pattern was significantly associated with postoperative biochemical remission ($P < .05$). Among 64 patients in whom the granulation pattern could be determined, biochemical remission was achieved in 24 of 27 patients (88.9%) with dense granular adenoma, compared with 19 of 37 patients (51.4%) with sparse granular adenoma. Preoperative and

Table 1. Preoperative Characteristics of Patients with Acromegaly

Characteristics	Overall Patients (n = 68)	Remission (n = 44)	Non-remission (n = 24)	*P*
Sex, female, n (%)	37 (54.4)	25 (56.8)	12 (50.0)	.77
Age at diagnosis (years)	43.80 ± 11.82	46.09 ± 11.74	39.70 ± 11.10	.03
BMI (kg/m^2)	29.41 ± 4.67	29.50 ± 5.02	29.24 ± 4.07	.80
Diabetes, n (%)	31 (45.6)	19 (43.2)	12 (50.0)	.78
Hypertension n (%)	29 (42.6)	20 (45.4)	9 (37.5)	.70
Adenoma size (mm)	14.0 (11.75-24.25)	12.0 (11.0-20.0)	22.0 (12.25-33.0)	.008
Microadenomas (<10 mm), n%	9 (13.2)	9 (20.4)	0 (0)	.03
Macroadenomas (10-39.9mm) n, %	54 (79.4)	34 (77.3)	20 (83.3)	.03
Giant adenomas (≥40 mm) n, %	5 (7.4)	1 (2.3)	4 (16.6)	.03
Morning cortisol (µg/dL)	14.0 (10.30-16.79)	14.0 (10.55-16.71)	13.70 (10.12-18.42)	.59
ACTH (pg/mL)	25.0 (17.50-40.43)	25.05 (16.07-39.55)	26.40 (18.10-41.35)	.96
Prolactin (ng/mL)	12.0 (7.30-29.58)	11.35 (7.00-31.27)	12.80 (8.95-24.85)	.92
TSH (µIU/mL)	1.41 (0.96-1.80)	1.50 (1.02-2.20)	1.35 (0.81-1.69)	.18
Free T4 (ng/dL)	0.90 (0.82-1.20)	0.95 (0.82-1.20)	0.90 (0.79-1.15)	.34
FSH (IU/L)	7.10 (3.80-17.10)	8.20 (4.30-42.40)	4.95 (2.90-10.20)	.06
LH (IU/L)	4.50 (2.35-13.06)	5.10 (3.40-19.90)	2.50 (0.90-5.75)	.01
Serum 25(OH) vitamin D (ng/mL)	17.0 (13.0-21.50)	16.70 (13.0-20.75)	17.0 (13.0-23.0)	.68
Serum creatinine (mg/dL)	0.67 ± 0.15	0.68 ± 0.15	0.65 ± 0.14	.31
Preoperative steroid coverage, n (%)	7 (10.3)	2 (4.5)	5 (20.8)	.08
Preoperative hypothyroidism, n (%)	5 (7.4)	4 (9.1)	1 (4.2)	.31
Preoperative hypogonadism, n (%)	18 (26.4)	6 (13.6)	12 (50.0)	.003
Postoperative hypothyroidism, n (%)	9 (13.2)	3 (6.8)	6 (25.0)	.06
Postoperative hypocortisolism, n (%)	11 (16.1)	5 (11.3)	6 (25.0)	.14
Postoperative hypogonadism, n (%)	15 (22.0)	6 (13.6)	9 (37.5)	.02

Data are presented as mean ± SD or median (interquartile range [IQR]) as appropriate.
ACTH, adrenocorticotropic hormone; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

postoperative hypogonadism was more common in the non-remission group than in the remission group ($P < .05$). In contrast, preoperative and postoperative hypothyroidism and hypocortisolism did not differ between groups ($P > 0.05$).

Preoperative and First-Year Postoperative Results

Biochemical parameters measured preoperatively and during follow-up are shown in Table 2. Preoperative GH, IGF-1, and Ca levels were higher in the non-remission than the remission group ($P < .05$), whereas serum P levels were similar ($P = .24$). On POD_{2-4} and at month 3, GH, IGF-1, Ca, and P levels remained higher in the non-remission group (all $P < .05$). At month 12, GH and IGF-1 levels were still higher in the non-remission group (both $P < .001$), whereas Ca and P levels did not differ between groups ($P = .67$ and $P = .20$, respectively).

Biochemical parameters changed significantly within 1 year after surgery (Figure 1). Friedman tests demonstrated significant longitudinal changes in GH, IGF-1, and IGF-1 ULN levels in both remission and non-remission groups. Post hoc pairwise comparisons with Bonferroni adjustment revealed that GH levels at POD_{2-4}, 3 months, and 12 months were significantly lower than preoperative values in both groups. Growth hormone levels at POD_{2-4}, 3 months, and 12 months were all significantly lower than preoperative values (all $P < .05$). In the remission group, there were no significant differences across postoperative time points, whereas in the non-remission group, GH at 12 months was lower than at POD_{2-4} ($P = .017$).

Insulin-like growth factor-1 showed different trends by remission status. In the remission group, IGF-1 decreased significantly at POD_{2-4}, 3 months, and 12 months compared to preoperative values (all $P < .001$), with further decreases at 3 and 12 months. In non-remission, significant decreases were seen only at 3 and 12 months ($P < .001$), whereas POD_{2-4} was not significant ($P = .061$). Insulin-like growth factor-1 upper limit of normal ratio also declined after surgery in both groups, with further reductions at later time points, especially in the remission group ($P = .001$). In non-remission, only the 12-month value was lower than the POD_{2-4} value ($P = .013$).

Changes in Ca levels followed a less consistent pattern during the 1-year follow-up period. Calcium levels decreased significantly at POD_{2-4} compared with preoperative values in both the remission and non-remission groups ($P < .05$ for both). During the follow-up period, Ca levels in both groups were significantly higher than POD_{2-4} values at month 3 ($P < .05$). At month 12, Ca levels in the remission group remained significantly higher than POD_{2-4} values ($P < .05$). Phosphorus levels were significantly lower than preoperative values

Table 2. Comparison of Preoperative, Early Postoperative Days, 3rd Month and 12th Month Biochemical Parameters and Remission Status of Patients with Acromegaly

Variable	Remission Group (n = 44)	Non-remission Group (n = 24)	*P*
Preoperative values			
GH (ng/mL)	4.55 (2.45-8.91)	11.75 (5.14-22.37)	.001
IGF-1 (ng/mL)	443.50 (376.75-603.75)	647.00 (492.75-835.25)	.001
IGF-1 ULN	2.00 (1.60-3.07)	2.78 (2.20-3.67)	.006
Serum calcium (mg/dL)	9.52 ± 0.40	9.89 ± 0.52	.005
Serum phosphorus (mg/dL)	4.49 ± 0.53	4.67 ± 0.69	.24
POD_{2-4} values	POD_{2-4} values	POD_{2-4} values	
GH (ng/mL)	0.79 (0.40-1.35)	2.55 (1.62-7.59)	<.001
IGF-1 (ng/mL)	189.10 (152.50-283.85)	454.50 (372.25-611.20)	<.001
IGF-1 ULN	0.91 (0.70-1.20)	2.03 (1.68-2.34)	<.001
Percentage decrease in IGF-1 (%)	52.1 ± 19.3	28.5 ± 23.6	<.001
Serum calcium (mg/dL)	8.97 ± 0.34	9.51 ± 0.55	<.001
Percentage decrease in calcium (%)	5.7 ± 4.2	2.6 ± 6.3	.10
Serum phosphorus (mg/dL)	3.82 ± 0.62	4.28 ± 0.52	.007
Percentage decrease in phosphorus (%)	13.9 ± 16.4	4.6 ± 12.9	.03
3rd month values	3rd month values	3rd month values	
GH (ng/mL)	0.59 (0.14-1.36)	1.76 (1.20-4.85)	<.001
IGF-1 (ng/mL)	162.32 ± 63.89	402.04 ± 166.71	<.001
IGF-1 ULN	0.69 ± 0.24	1.65 ± 0.66	<.001
Serum calcium (mg/dL)	9.46 ± 0.46	9.72 ± 0.35	.010
Serum phosphorus (mg/dL)	3.63 ± 0.52	4.29 ± 0.66	<.001
12th month values	12th month values	12th month values	12th month values
GH (ng/mL)	0.58 (0.33-1.48)	1.45 (0.58-3.69)	.010
IGF-1 (ng/mL)	154.49 ± 62.82	335.63 ± 213.75	<.001
IGF-1 ULN	0.67 ± 0.26	1.36 ± 0.78	<.001
Serum calcium (mg/dL)	9.47 ± 0.40	9.43 ± 0.34	.67
Serum phosphorus (mg/dL)	3.52 ± 0.50	3.67 ± 0.47	.20

Data are presented as median [interquartile range (IQR)] for non-normally distributed variables and mean ± SD for normally distributed variables. *P* values indicate comparisons between groups (Mann–Whitney *U*-test or independent-samples *t*-test, as appropriate).
GH, growth hormone; IGF-1, insulin-like growth factor-1; IGF-1 ULN, the ratio of insulin-like growth factor-1 upper limit of normal; POD_{2-4}, postoperative 2-4 days.

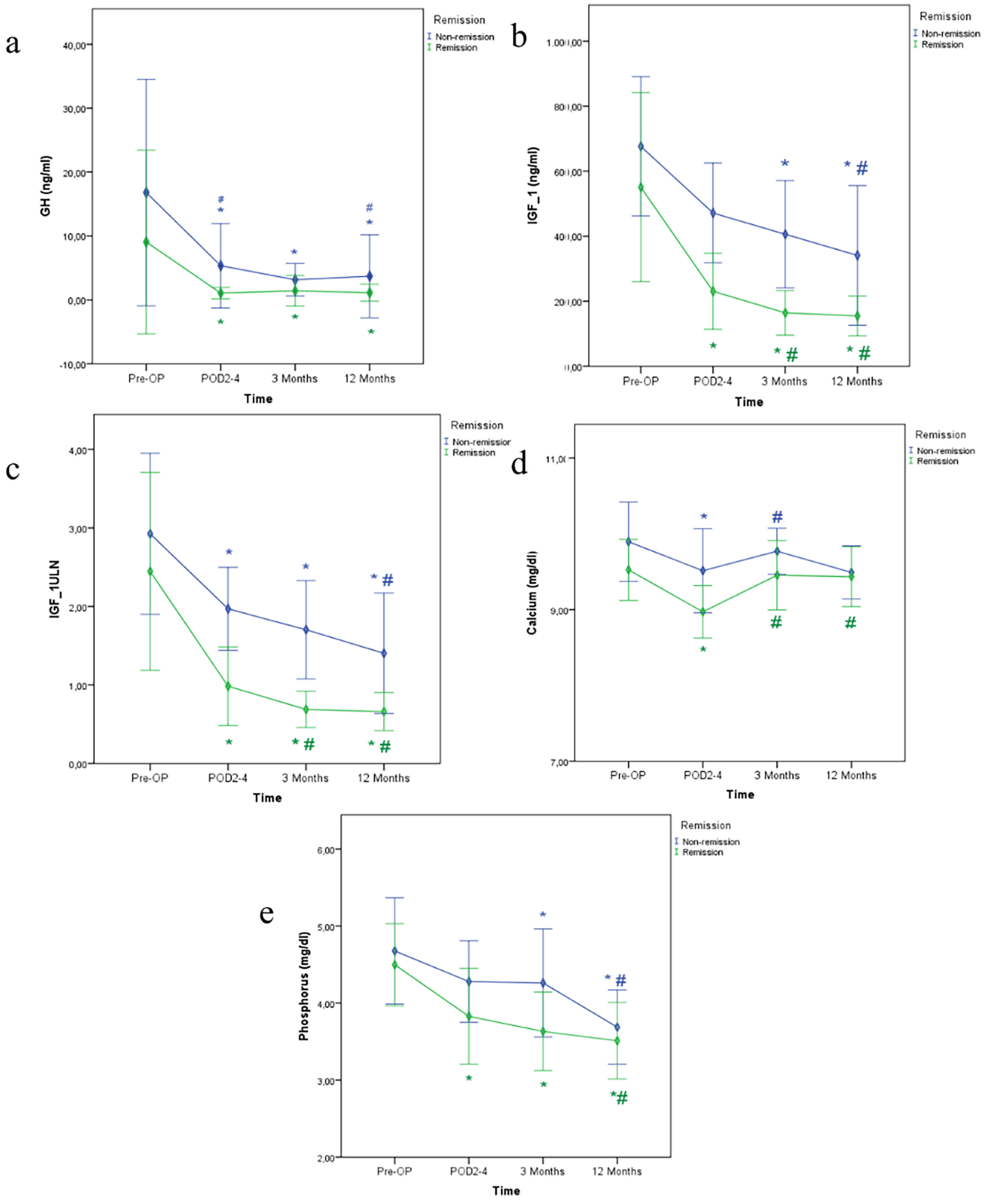

Figure 1. Time course of GH, IGF-1, IGF-1 ULN, calcium, and phosphorus in the remission and non-remission groups from the preoperative period to month 12 after surgery. POD_{2-4}, postoperative days 2-4; GH, growth hormone; IGF-1, insulin-like growth factor-1; ULN, upper limit of normal. *$P < .05$ vs. preoperative values; #$P < .05$ vs. POD_{2-4} values.

Table 3. The Correlation Analysis Between Age at Diagnosis, Adenoma Size, and Biochemical Parameters Measured in POD_{2-4}

	Age of Diagnosis	Adenoma Size	GH	IGF-1	IGF-1 ULN	Calcium	Phosphorus
Age of diagnosis	1	—	—	—	—	—	—
Adenoma size	−0.42** (<0.001)	1	—	—	—	—	—
GH	−0.36** (0.003)	0.43** (<0.001)	1	—	—	—	—
IGF-1	−0.39** (0.001)	0.18 (0.13)	0.65** (<0.001)	1	—	—	—
IGF-1 ULN	−0.19 (0.12)	0.19 (0.11)	0.63** (<0.001)	0.91** (<0.001)	1	—	—
Calcium	−0.16 (0.20)	0.24 (0.05)	0.17 (0.16)	0.28* (0.02)	0.28* (0.03)	1	—
Phosphorus	−0.40** (0.001)	0.26* (0.03)	0.33* (0.01)	0.37** (0.003)	0.35** (0.006)	0.32* (0.01)	1

GH, growth hormone; IGF-1, insulin-like growth factor 1; IGF-1 ULN, the ratio of IGF-1 upper limit of normal, Spearman correlation analysis.
*$P < .05$.
**$P < .01$.

at all follow-up time points in the remission group ($P < .05$). In the non-remission group, however, a significant reduction compared with preoperative values was observed only at 3 and 12 months ($P < .05$), whereas the difference at POD_{2-4} was not statistically significant ($P > .05$). Furthermore, only the 12-month P level was significantly lower than both the preoperative and POD_{2-4} values ($P < .05$).

In the first MRI performed 3 months after surgery, residual adenomatous tissue was detected in 14 (58.3%) of the 24 patients who did not achieve biochemical remission. After multidisciplinary evaluation, patients without radiologically detectable residual tumor and those with residual adenoma at high risk for reoperation (n = 4) received somatostatin analogs and/or cabergoline, whereas the remaining patients with residual adenoma were managed with medical therapy before considering reoperation. Of the 68 patients, 47 did not require postoperative pituitary hormone replacement, whereas 21 required replacement for at least 1 hormone. Multiple pituitary hormone deficiencies requiring replacement were present in 7 patients; isolated glucocorticoid, thyroid hormone, and sex hormone replacement was initiated in 4, 2, and 8 patients (testosterone, n = 6; estrogen/progesterone, n = 2), respectively. Glucocorticoid and thyroid hormone replacement began after the POD_{2-4} biochemical measurements, whereas sex hormone replacement began after the 3-month evaluation. At the 12-month evaluation, 7 of the 24 patients receiving medical therapy achieved biochemical remission. Because only 7 patients achieved remission after adjuvant treatment, the authors did not perform a separate analysis by 12-month remission status.

Predictive Performance of Postoperative Days 2-4 Biochemical Parameters

The correlation analysis between age at diagnosis, adenoma size, and POD_{2-4} GH, IGF-1, Ca, and P is shown in Table 3. A significant negative correlation was found between age at diagnosis and adenoma size, GH, IGF-1, and P ($P < .001$, $P = .003$, $P = .001$, and $P = .001$, respectively). Adenoma size was positively correlated with GH and P ($P < .001$ and $P = .03$, respectively). Growth hormone was significantly correlated with IGF-1, IGF-1 ULN, and P ($P < .001$, $P < .001$, and $P = .01$, respectively). Insulin-like growth factor-1 and IGF-1 ULN were positively correlated with Ca and P (IGF-1: $P = .02$ and $P = .003$; IGF-1 ULN: $P = 0.03$ and $P = .006$, respectively).

Table 4 summarizes the results of the ROC analysis for the parameters measured on POD_{2-4} and their corresponding predictive performances. A GH cut-off of ≤1.28 ng/mL showed the best predictive value for remission on POD_{2-4} (AUC = 0.858, 95% CI: 0.77-0.94, sensitivity = 0.74, specificity = 0.88). A cut-off of ≤2.50 ng/mL achieved 95.2% sensitivity, whereas a cut-off of ≤1.01 ng/mL achieved 95.8% specificity. Insulin-like growth factor-1 showed the next highest discriminatory ability, with a 45.29% decrease (AUC = 0.816, 95% CI: 0.71-0.92, sensitivity = 0.73, specificity = 0.79). For IGF-1 percentage decrease, a cut-off of ≥14.2% provided 95.1% sensitivity, while ≥63.4% provided 95.8% specificity. Although P showed higher predictive accuracy than Ca (AUC = 0.647, 95% CI: 0.50-0.78, sensitivity = 0.60, specificity = 0.74 vs. AUC = 0.614, 95% CI: 0.45-0.77, sensitivity = 0.56, specificity = 0.57), both had lower discriminatory ability than GH and IGF-1. The best POD_{2-4} ROC curves are shown in Figure 2. Among the 68 patients, postoperative GH and IGF-1 were measured on POD_2 in 3 patients and POD_4 in 5; therefore, a sensitivity analysis was performed in the remaining 60 patients with POD_3 measurements. For POD_3 GH, a cut-off of ≤1.28 ng/mL showed good discrimination for remission (AUC = 0.897, 95% CI: 0.822-0.973, sensitivity = 0.74, specificity = 0.95, Youden index = 0.69). For the percentage decrease in POD_3 IGF-1, a cut-off of ≥45.30% showed good discrimination for remission (AUC = 0.784, 95% CI: 0.664-0.905, sensitivity = 0.74, specificity = 0.71, Youden index = 0.45). These findings were consistent with those of the overall POD_{2-4} cohort.

Multivariable Analysis of Factors Associated with Remission

Multivariable logistic regression was performed to assess the association between early postoperative biochemical parameters and

Table 4. ROC Analyses of POD_{2-4} GH Levels and Percentage Decreases in IGF-1, Calcium, and Phosphorus for Predicting Biochemical Remission

Parameter	Cut-off Points	AUC	%95 CI	Sensitivity %	Specificity %	Youden Index
GH*	1.28	0.858	0.77-0.94	0.74	0.88	0.62
IGF-1** (%)	45.29	0.816	0.71-0.92	0.73	0.79	0.52
Calcium** (%)	5.18	0.614	0.45-0.77	0.56	0.57	0.12
Phosphorus** (%)	10.50	0.647	0.50-0.78	0.60	0.74	0.33

AUC, area under the curve; GH, growth hormone; IGF-1, insulin-like growth factor-1; ROC, receiver operating characteristic.
*GH cut-off values are expressed in ng/mL.
**IGF-1, calcium, and phosphorus cut-off values are expressed as the percentage decrease from preoperative levels to POD2-4.

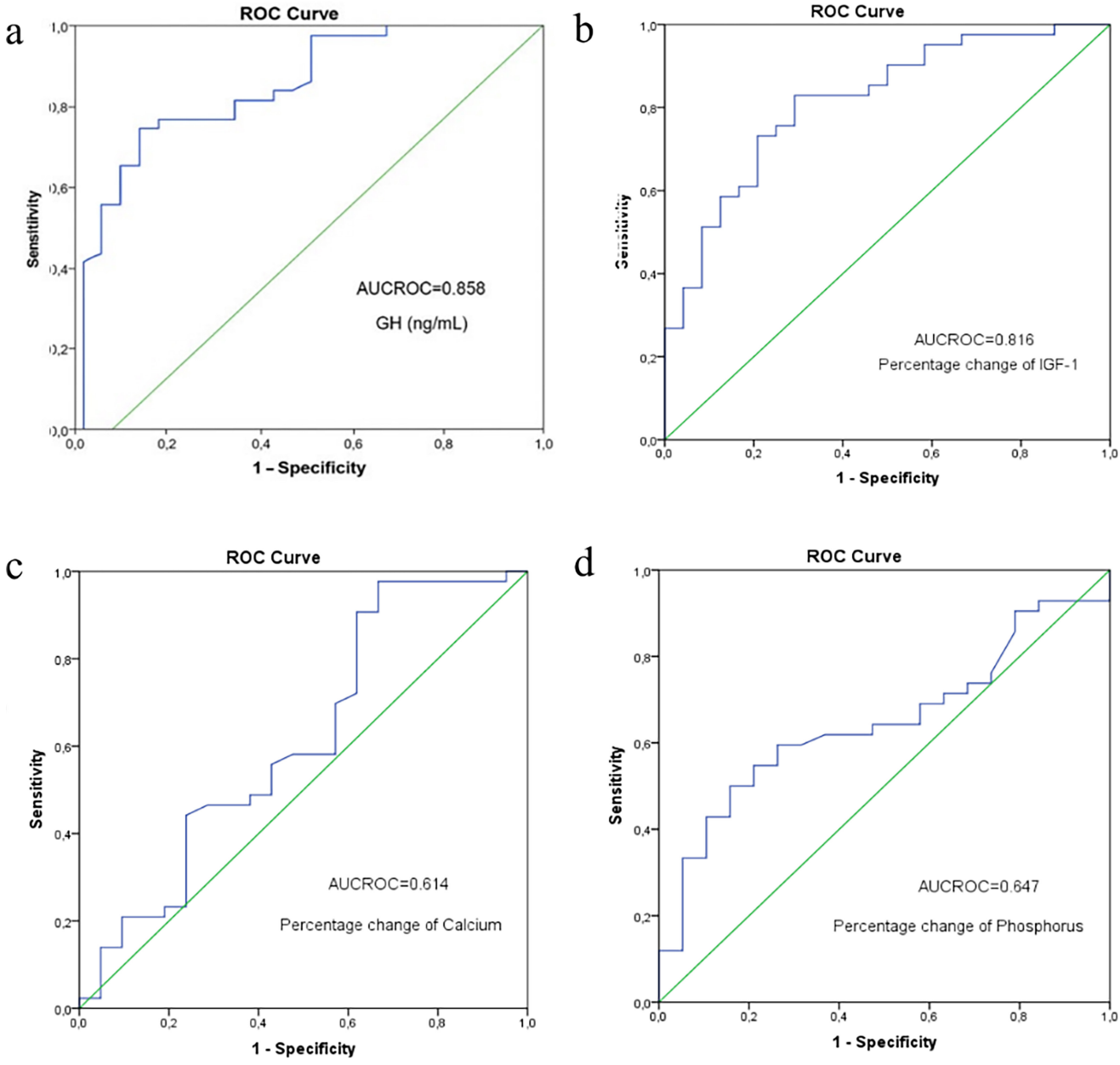

Figure 2. ROC curves for biochemical remission using POD_{2-4} GH and percentage decreases in IGF-1, calcium, and phosphorus. ROC analyses were based on POD_{2-4} GH and percentage decreases in IGF-1, calcium, and phosphorus. POD_{2-4}, postoperative days 2-4; GH, growth hormone; IGF-1, insulin-like growth factor-1.

biochemical remission (Table 5). In Model 1, lower POD_{2-4} GH levels were independently associated with biochemical remission (OR = 0.249, 95% CI: 0.102-0.609, *P* = .002). Sparsely granulated adenomas had lower odds of remission than densely granulated adenomas (OR = 0.085, 95% CI: 0.011-0.677, *P* = 0.020). In Model 2, the percentage decrease in IGF-1 was independently associated with remission (OR = 1.046 per 1% decrease, 95% CI: 1.010-1.084, *P* = .013), and sparsely granulated adenomas were also associated with lower

Table 5. Multivariable Logistic Regression Analyses for Predictors of Biochemical Remission in POD_{2-4} Measurements

Variable	Model 1 (GH) OR (95% CI)	*P*	Model 2 (IGF-1 %) OR (95% CI)	*P*
Age at diagnosis	0.990 (0.918-1.067)	.790	1.010 (0.948-1.076)	.758
Adenoma size	0.968 (0.894-1.049)	.429	0.960 (0.890-1.035)	.286
Granulation pattern (sparsely vs. densely granulated)	0.085 (0.011-0.677)	.020	0.147 (0.030-0.730)	.019
POD_{2-4} GH	0.249 (0.102-0.609)	.002		
Percentage decrease in IGF-1 (%)	—	—	1.046 (1.010-1.084)	.013

GH, growth hormone; IGF-1, insulin-like growth factor-1; OR, odds ratio; POD_{2-4}, postoperative days 2-4.

odds of remission (OR = 0.147, 95% CI: 0.030-0.730, $P = 0.019$). Age at diagnosis and adenoma size were not associated with remission in either model.

Discussion

In this study, the authors evaluated the levels of GH, IGF-1, Ca, and P at postoperative POD_{2-4}, 3 months, and 12 months in patients with newly diagnosed acromegaly. The authors investigated whether the values of these parameters on POD_{2-4} contributed to the prediction of biochemical remission.

The study found that POD_{2-4} GH levels were associated with remission and demonstrated good discriminative ability in newly diagnosed patients with acromegaly. Previous studies have suggested that GH levels measured within the first postoperative week can predict remission, but the appropriate timing and cut-off values have varied among reports.[22,23] Some studies have shown that GH levels on the first postoperative day are a good predictor of remission and an effective parameter,[23–25] and particularly emphasized that this predictive value is better on the first postoperative day than on the second postoperative day.[26] Although there is no definitively established or recommended cut-off value, a random GH level <1-1.6 ng/mL or nadir GH <0.4-1 ng/mL in the early postoperative period (24 hours-5 days) has been shown to be associated with long-term remission with a high positive predictive value in many studies.[25,27] Conversely, GH ≥1.5-2 ng/mL on the first postoperative day has been associated with persistent disease or the need for additional treatment in most series.[22,25,26] The POD_{2-4} GH levels observed in the cohort were broadly consistent with those reported previously, suggesting that early postoperative GH assessment may be helpful for early risk stratification.

In this study, the authors also assessed IGF-1's predictive performance for remission using the percentage decrease in IGF-1 at POD_{2-4} relative to preoperative values. The authors considered this approach to be more informative than absolute postoperative IGF-1 values because of the delayed normalization of IGF-1 after surgery and its longer half-life. Using this approach, the authors found that the percentage decrease in IGF-1 showed good discriminative performance for remission. This study is one of the few to investigate the predictive value of early postoperative IGF-1 for remission, as existing evidence has largely focused on GH measurements, with limited data available on the potential role of IGF-1 during the first postoperative week. Hazer et al[28] demonstrated the potential of a first-week postoperative IGF-1 decrease (14.4%) to predict remission, although the 1-month decrease (51.1%) showed better predictive performance. Similarly, Cetinalp et al[29] found that postoperative day 1 GH and tumor volume were independent predictors of remission and that both GH and IGF-1 measured during the first postoperative week showed high discriminatory performance. As in this study, postoperative GH and IGF-1 levels differed significantly between the remission and non-remission groups during follow-up (up to 6 months). Both studies also demonstrated differences in IGF-1 reduction according to remission status on POD_1 and during the first postoperative week, although its predictive performance was lower than that of GH.[28,29] In the study by Sakata et al[30], POD_1 GH and POD_{14} nadir GH measurements were good predictors of remission. Furthermore, although POD_1 IGF-1 levels did not differ significantly by remission status, POD_{14} IGF-1 showed good predictive value for both endocrinological improvement and the need for additional treatment. In the study by Wang et al[31], IGF-1 and nadir GH were evaluated on POD_{2-5}; however, the prognostic assessment was primarily based on GH, and no independent predictive analysis of IGF-1 was reported.

The observed association between early postoperative IGF-1 changes and remission may be partly explained by postoperative IGF-1 kinetics. Early postoperative IGF-1 is generally not measured because of its long half-life. Total IGF-1 has a half-life of approximately 12-15 hours in individuals with a normal GH–IGF-1 axis.[32,33] Although large cohort studies evaluating postoperative IGF-1 half-life in acromegaly are lacking, 1 study measured GH and IGF-1 daily for 72 hours after surgery in 28 patients and reported a mean (SD) postoperative IGF-1 half-life of 55 (19) hours. IGF-1 decreased to <65% of preoperative values by POD2 in patients who achieved remission.[10] The POD_{2-4} assessment closely corresponds to this estimated half-life. Hazer et al[28] also reported that IGF-1 decreased by up to 25% on POD1 and 50% during the first postoperative week in most patients. Although guidelines recommend waiting up to 12 weeks after surgery to assess remission, several studies and the findings of this study suggest that early postoperative decreases in IGF-1 are more pronounced in patients who achieve remission. The authors suggest that an early postoperative decrease in IGF-1 may provide clinically relevant information and be potentially helpful for early risk stratification of subsequent remission status. Therefore, further research is needed to clarify the significance of the percentage decrease in IGF-1 at POD_{2-4} relative to the preoperative value.

The authors also evaluated 1-year follow-up results from the preoperative baseline. Growth hormone and IGF-1 levels gradually decreased in both groups over the follow-up period, reaching their lowest values at 1 year. In the non-remission group, this decline was likely attributable to medical treatment initiated during follow-up.

Calcium and P, which are influenced by the GH–IGF-1 axis, were also evaluated. Phosphorus and Ca levels were significantly higher in the non-remission group than the remission group at POD_{2-4} and 3 months, but this difference disappeared by 1 year. This finding may reflect reduced GH/IGF-1-mediated metabolic activity following medical treatment initiated 3-6 months postoperatively in patients without biochemical remission. Previous studies have shown that P, measured preoperatively or at least 3-6 months after surgery,[3] differs according to remission status in acromegaly, and that baseline phosphorus levels may have predictive value.[34,35] To the authors' knowledge, no studies have evaluated early postoperative changes in P and Ca in response to declining GH and IGF-1. Although P and Ca decreased with GH and IGF-1 and were higher in the non-remission group, their predictive value at POD_{2-4} was limited. Thus, POD_{2-4} decreases in Ca and P appear to reflect early biochemical changes but have lower predictive value than GH and IGF-1. Because routine postoperative care includes a 2–3-day hospital stay, measuring GH and IGF-1 at POD_{2-4} may help assess early remission.

The main limitations of this study are the rarity of acromegaly and the relatively small sample size, given the retrospective design. The cohort was limited by the inclusion of only untreated patients and the strict inclusion criteria. Due to the retrospective nature of the study, vitamin D measurements could not be obtained from an adequate number of patients during the follow-up period and, therefore, could not be evaluated in analyses at subsequent time points. Moreover, undocumented vitamin D supplementation could not be entirely

excluded. Furthermore, serum alkaline phosphatase, parathyroid hormone, and bone turnover markers could not be included in the analyses because of insufficient data availability. As a limitation, while the potential effects of postoperative hormone replacement therapies and perioperative stress-dose glucocorticoid administration on Ca–P metabolism are thought to be limited, they cannot be entirely excluded. Similarly, when evaluating parameters measured in the early postoperative period (POD_{2-4}), the lack of a standard measurement day, due to retrospective data collection, is considered a weakness of the study. However, new analyses, which included only POD_3 patients to assess potential impact, particularly on GH levels, also appeared consistent with the study's main finding.

In conclusion, GH, IGF-1, Ca, and P levels measured on POD_{2-4} were higher in patients who did not achieve remission than in those who did. Among these biochemical parameters, postoperative GH levels and the percentage decrease in IGF-1 may be helpful for early risk stratification. The association of changes in Ca and P with remission was less pronounced than that of GH and IGF-1. The potential role of these parameters in the early postoperative assessment of remission in patients with acromegaly may be further clarified by future studies.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence Tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Gazi University (Approval no: E-77082166-604.01-1174274, Date: February 19, 2025).

Informed Consent: Informed consent is not applicable for this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.B., F.Y., M.C., M.M.Y., E.C., F.T., A.A., M.A.K., E.T.C., M.A., O.O.; Design – A.B., M.C., M.M.Y., E.C., M.A.; Supervision – A.A., F.T., M.A.K., M.M.Y., E.T.C., M.A.; Resources – A.B., M.C., F.Y., O.O.; Materials – A.B.; Data Collection and/or Processing – A.B., M.A.; Analysis and/or Interpretation – S.Y., A.B.; Literature Search – A.B., M.A., A.A.; Writing – A.B, M.A.; Critical Review – F.B., A.A., M.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support. Müjde Aktürk is a member of the International Editorial Board of Endocrinology Research and Practice. However, she was involved in this manuscript solely as an author and did not participate in any stage of the editorial evaluation or decision-making process.

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