Cerrahpaşa Med J 2026; 50: 1-7 ORIGINAL ARTICLE

Prolactin Co-Staining in Acromegaly: Clinical Features and Long-Term Outcomes

Cem Sulu[1], Necmettin Tanrıöver[2,3], Cansu Türker Sarıçoban[4], Nurperi Gazioğlu[2,3], Pınar Kadıoğlu[1,3]

[1]Division of Endocrinology-Metabolism and Diabetes, Department of Internal Medicine, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[2]Department of Neurosurgery, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[3]Pituitary Center, İstanbul University-Cerrahpaşa, İstanbul, Türkiye
[4]Department of Medical Pathology, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Cite this article as: Sulu C, Tanrıöver N, Sarıçoban CT, Gazioğlu N, Kadıoğlu P. Prolactin co-staining in acromegaly: clinical features and long-term outcomes. *Cerrahpaşa Med J* 2026, 50, 0096, doi: 10.5152/cjm.2026.26096.

What is already known on this topic?

- *Growth hormone–secreting pituitary adenomas may show prolactin (PRL) co-staining.*
- *The prognostic significance of PRL co-staining in acromegaly remains unclear.*

What does this study add on this topic?

- *In this large single-center cohort, growth hormone– and prolactin-positive pituitary adenomas accounted for approximately one-third of acromegaly cases.*
- *Growth hormone– and prolactin-positive tumors showed lower growth hormone levels and less frequent cavernous sinus invasion than growth hormone–only adenomas.*
- *Prolactin co-staining was not an independent predictor of surgical remission or long-term biochemical control, suggesting that prognosis should be interpreted together with tumor- and treatment-related factors.*

Abstract

Objective: To compare the clinical presentation, tumor characteristics, surgical remission, and long-term biochemical control between patients with growth hormone (GH) and prolactin (PRL) co-staining pituitary adenomas (GH&PRL-PAs) and those with merely growth hormone–secreting pituitary adenomas (GH-PAs).

Methods: This retrospective, single-center cohort included adults with acromegaly who underwent transsphenoidal surgery between 2000 and 2023. GH&PRL-PAs were defined by positive immunostaining for both GH and PRL. Predictors of surgical remission were assessed using multivariable logistic regression, and determinants of last-visit insulin-like growth factor 1 (IGF-1) were evaluated using multivariable linear regression.

Results: Among 358 patients, 125 patients (34.9%) were classified as GH&PRL-PAs. Median follow-up was 103 [51-144] months. Women comprised 59.2% of the cohort; female sex was similarly distributed between GH&PRL-PAs and GH-PAs (54.4% vs. 61.8%, $P = .174$). GH&PRL-PAs had lower GH levels at diagnosis (6.3 [3.2-23] vs. 12.4 [5-29.7] ng/mL, $P = .023$), postoperatively (1.2 [0.3-3.9] vs. 2.2 [0.3-3.9] ng/mL, $P = .021$), and at the last visit (1.2 [0.5-3.3] vs. 1.4 [0.6-3.6] ng/mL, $P = .006$). Insulin-like growth factor 1 levels were comparable at diagnosis and the last visit. Tumor size and Ki-67 index were similar, whereas cavernous sinus invasion was less frequent in GH&PRL-PAs (39.8% vs. 53.1%, $P = .027$). Surgical remission neither differed significantly between groups (37.6% vs. 28.8%, $P = .087$) nor did active disease at the last visit (17.6% vs. 17.2%, $P = .918$). Prolactin staining was not an independent predictor of surgical remission or last-visit IGF-1.

Conclusion: Growth hormone and prolactin co-staining pituitary adenomas show a distinct hormonal profile, but PRL co-staining alone does not appear to determine surgical or long-term biochemical outcomes.

Keywords: Acromegaly, growth hormone, immunohistochemistry, pituitary adenoma, prolactin, treatment

Introduction

Acromegaly is a rare, chronic disorder caused by a growth hormone–secreting pituitary adenoma (GH-PA).[1] Although the classic pathological profile is monohormonal growth hormone (GH) expression, up to one-third of somatotroph tumors also show prolactin (PRL) immunoreactivity. Co-secreting GH and PRL pituitary adenoma (GH&PRL-PA) can reflect different pathological entities, including mixed adenomas with distinct somatotroph and lactotroph cell populations, mammosomatotroph tumors arising from a shared progenitor lineage, and the rarer acidophil stem cell tumors.[2,3] Despite this established pathological framework, data on the clinical course of acromegaly, surgical and medical outcomes, and potential predictors of biochemical control in GH&PRL-PA remain limited, and findings are inconsistent.[4-9]

In this study, the authors analyzed whether patients with GH&PRL-PAs differ from those with GH-PAs in terms of clinical presentation, biochemical and radiological tumor characteristics, surgical

Received: June 23, 2026 **Revision Requested:** July 6, 2026 **Last Revision Received:** July 7, 2026 **Accepted:** July 13, 2026 **Publication Date:** August 24, 2026
Corresponding author: Pınar Kadıoğlu, Division of Endocrinology-Metabolism and Diabetes, Department of Internal Medicine, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye; Pituitary Center, İstanbul University-Cerrahpaşa, İstanbul, Türkiye **e-mail:** kadioglup@yahoo.com
DOI: 10.5152/cjm.2026.26096

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

cure, and long-term biochemical control. The aim is to determine whether PRL co-staining identifies a clinically distinct subgroup with different disease behavior and prognosis, which can inform treatment planning and patient counseling.

Methods

Study Design and Setting

This single-center, retrospective cohort study was conducted at the Pituitary Center of a tertiary-care university hospital. The study was approved by the Clinical Research Ethics Committee of İstanbul University - Cerrahpaşa under the broader retrospective acromegaly cohort protocol (Approval No.: 692023 Date: May 22, 2023). All procedures conformed to the Declaration of Helsinki. The study was reported in accordance with the STROBE guideline. Written informed consent was obtained from patients who participated in this study.

Study Population

The authors reviewed the records of consecutive adults diag-nosed with acromegaly and managed at this center between 2000 and 2023 (total cohort, N = 607). Eligibility required a defini-tive diagnosis of acromegaly; transsphenoidal surgery (TSS) with histopathological confirmation; availability of core clinical, bio-chemical, radiological, and pathological data; and postoperative follow-up of at least 12 weeks. Patients were excluded if documen-tation was insufficient to determine tumor size or if pathological features precluded valid interpretation of immunohistochemistry (IHC) (e.g., predominantly cystic morphology, extensive hemor-rhage, or necrosis).

Data Sources and Variables

Data were abstracted from electronic and paper charts; when key fields were missing, information was cross-checked in the national electronic health record system (e-Nabız, available since 2015). The authors recorded demographics (age and sex), comorbidities (diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and malignancy), and treatment information, including preoperative and postoperative therapies for acromegaly. Imaging variables included maximal tumor diameter on preoperative magnetic resonance imaging and the presence/grade of cavernous sinus invasion. Endocrine assessments comprised GH and IGF-1 at baseline, at the postoperative visit (≈12 weeks), and at the last available visit, together with evaluation of adrenal, thyroid, and gonadal axes.

Endocrine Evaluation, Follow-Up, and Definitions

Diagnosis, treatment, and follow-up adhered to international guidelines applicable at the time of care.[10-15] Preoperative medi-cal therapy with a long-acting somatostatin receptor ligand (SLAR) was initiated when the anticipated waiting period for transs-phenoidal surgery exceeded 1 month. All operations were per-formed via a transsphenoidal approach by 2 experienced pituitary neurosurgeons.

Routine postoperative assessment was scheduled at approxi-mately 12 weeks. Patients in remission were typically followed up every 6-12 months. In patients with persistent disease, further management, including repeat TSS, SLARs, cabergoline, pegviso-mant, and/or radiotherapy, was individualized according to dis-ease activity and guideline-based targets. Long-term biochemical control at the last visit was defined as normalization of IGF-1.

Follow-up duration was calculated from surgery to the last visit. Overall disease duration was calculated from the reported onset of acromegaly-related signs or symptoms to the last clinical contact.

Assays and Laboratory Methods

All hormonal measurements were performed in the central laboratory and interpreted using age-, sex-, assay-, and period-specific reference intervals. During the study period, GH and IGF-1 were measured using immunoradiometric assays before 2011, chemiluminescence immunoassays between 2011 and 2019, and electrochemiluminescence immunoassays from 2020 onward.

Pathological Study

Surgically excised specimens were immediately fixed in 10% neutral-buffered formalin, processed, and paraffin-embedded. Diagnosis was established on hematoxylin–eosin–stained sections. Pathology reports detailed IHC for GH, PRL, thyrotropin (TSH), adrenocorticotropin (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and Ki-67.

Statistical Analysis

Statistical analyses were conducted using SPSS version 29.0 (IBM SPSS Corp.; Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables are reported as mean ± standard deviation, whereas non-normally distributed variables are expressed as median and interquartile range. Categorical variables are presented as numbers and percentages. Comparisons between groups were performed using Student's *t* test or one-way ANOVA for normally distributed continuous variables, and the Mann–Whitney *U*-test or Kruskal–Wallis test for non-normally distributed variables, as appropriate. Categorical variables were compared using the Pearson χ^2 test or Fisher's exact test. Multivariable logistic regression analysis was performed to identify independent predictors of surgical remission. In addition, multivariable linear regression analysis was used to determine factors independently associated with last-visit IGF-1 levels. All statistical tests were 2-sided, and a P value <.05 was considered statistically significant.

Results

Patient Characteristics

A total of 358 patients with acromegaly were included, of whom 125 patients (34.9%) were classified as GH&PRL-PA. Median age at diagnosis was 39 years IQR [30-48], and 59.2% of patients were female. Macroadenomas were present in 78.5% of patients. The median follow-up duration was 103 months IQR [51-144], and the median disease duration was 138 months IQR [84-192].

Diabetes mellitus (36%) and hypertension (32.1%) were the most common comorbidities. Hypopituitarism was present at diagnosis in 11.5% of patients and in 26.5% of patients after TSS. Surgical remission after the initial TSS was achieved in 31.8% of patients. During follow-up, 57.8% received SLARs, 37.2% cabergoline, and 10.9% pegvisomant; 42.2% received combination therapy, most commonly SLARs plus cabergoline. Repeat TSS and radiotherapy were performed in 17.9% and 18.4% of patients, respectively. At the last visit, biochemical control was documented in 82.7% of patients.

Comparison Between Growth Hormone and Prolactin Co-Staining Pituitary Adenomas and Growth Hormone–Secreting Pituitary Adenomas

The baseline demographic and clinical characteristics of the groups are shown in Tables 1 and 2. Growth hormone levels were lower in GH&PRL-PAs at diagnosis, after TSS, and at the last visit. Tumor size and Ki-67 index were comparable between groups. However, cavernous sinus invasion was less frequent

Table 1. Comparison of the Clinical and Laboratory Features of Patients with Acromegaly

Features	GH&PRL-PA (n = 125)	GH-PA (n = 233)	*P**
Baseline features			
Age at diagnosis (years)	40.5 ± 11.2	39.5 ± 11.7	.428
Gender, female %	54.4	61.8	.174
GH at diagnosis (ng/mL)	6.3 [3.2-23]	12.4 [5-29.7]	.023
IGF-1 at diagnosis (ng/mL)	711 [522.7-933.5]	691 [511-946]	.875
IGF-1/ULN at diagnosis	2.5 [1.7-3.3]	2.3 [1.8-3]	.618
Max. tumor diameter (mm)	15 [11-24]	18 [12-25]	.727
Macroadenoma, (%)	82	87.6	.173
Histopathology			
Ki-67	1.5 [1-2.5]	1.5[1-2.5]	.962
Treatments, n (%)			
SLAR	67 (53.6)	140 (60.1)	.236
CBG	76 (35.2)	104 (38.2)	.576
PEG	15 (12)	24 (10.3)	.623
Radiotherapy, n (%)	19 (15.2)	47 (20.2)	.248
Repeat TSS, n (%)	20 (16)	44 (18.9)	.497
Response to treatment			
Postoperative GH (ng/mL)	1.2 [0.3-3.9]	2.2 [0.3-3.9]	.021
Postoperative IGF-1 (ng/mL)	305.2 [191.8-600]	351.7 [227.5-593]	.310
Postoperative remission, %	37.6	28.8	.087
Last status			
GH at last visit (ng/mL)	1.2 [0.5-3.3]	1.4 [0.6-3.6]	.006
IGF-1 at last visit (ng/mL)	182 [140.5-230.5]	185.5 [137-258.2]	.967
IGF-1/ULN at last visit	0.7 [0.5-1]	0.8 [0.6-1]	.731
Active disease, n (%)	22 (17.6)	40 (17.2)	.918
Total disease duration (months)	91 [40-135.5]	108 [60-144]	.049

Continuous data are presented as median [interquartile range] or mean ± SD.
CBG, cabergoline; GH, growth hormone; IGF-1, insulin-like growth factor-1; PEG, pegvisomant; SLAR, somatostatin receptor ligands; TSS, transsphenoidal surgery; ULN, upper limit of normal.
*Derived from chi-square and Mann–Whitney *U*-tests.

Table 2. Comorbidities of the Patients with Acromegaly

Features	Patients With Acromegaly (n = 358)	GH + PRL Group (n = 125)	GH Group (n = 233)	*P**
Hypertension, n (%)	115 (32.1)	42 (33.6)	73 (31.3)	.661
Diabetes mellitus, n (%)	129 (36)	40 (32)	89 (38.2)	.244
Dyslipidemia, n (%)	78 (21.8)	31 (24.8)	47 (20.2)	.312
Cardiovascular disease, n (%)	41 (11.5)	13 (10.4)	28 (12)	.647
Coronary artery disease, n (%)	32 (8.9)	10 (8)	22 (9.4)	.648
Congestive heart failure, n (%)	8 (2.2)	3 (2.4)	5 (2.1)	.702
Cerebrovascular disease, n (%)	9 (2.5)	3 (2.4)	6 (2.6)	.729
Cancer**, n (%)	34 (9.5)	15 (12)	19 (8.2)	.237

*Derived from chi-square test.
**4 patients with acromegaly had more than 1 cancer.

in GH&PRL-PAs than in GH-PAs (39.8% vs. 53.1%, *P* = .027). Comorbidities were similarly distributed between groups.

Predictors of Disease Control

In the multivariable linear regression model, male sex, higher Ki-67 index, and absence of postoperative remission were independently associated with higher last-visit IGF-1/ULN values (Table 3, Figure 1A). Lower baseline GH and IGF-1 levels were independently associated with a higher likelihood of surgical remission (Table 4, Figure 1B).

Discussion

In this study, GH&PRL-PAs represented approximately 35% of the cases. This subgroup exhibited consistently lower GH levels at diagnosis, postoperatively, and at last follow-up. Despite similar tumor sizes, cavernous sinus invasion was less frequent in the GH&PRL-PA group. However, PRL co-staining itself did not independently predict surgical remission or long-term disease control. Rather, long-term biochemical control was determined by female sex, a lower Ki-67 index, and achievement of surgical remission. Surgical remission, in turn, was predicted by lower baseline GH and IGF-1 levels.

The reported prevalence of GH&PRL-PAs in acromegaly varies considerably across studies, largely because of differences in diagnostic definitions. Overall, PRL co-secretion or co-expression has been described in approximately 25%-40% of patients with acromegaly.[4-6,9,16] In line with these data, PRL co-staining was observed in nearly 35% of the cohort. To the authors' knowledge, this represents the largest series from Türkiye evaluating both the frequency of PRL co-staining and its association with long-term outcomes in patients with acromegaly.

The findings of this study showed that GH&PRL-PAs and GH-PAs differ in hormonal profile. In this cohort, patients with GH&PRL-PAs tended to have lower GH levels at diagnosis, after TSS, and at the last visit, whereas IGF-1 levels were comparable between groups. This pattern is partly consistent with the study by Wang et al,[4] in which patients with acromegaly and hyperprolactinemia

Table 3. Predictors of Insulin-Like Growth Factor 1/Upper Limit of Normal at Last Visit

Predictor	B	Standard Error	*P*	95% CI for B
Baseline features				
Age at diagnosis	−0.001	0.003	.850	−0.007 to 0.005
Gender	0.217	0.068	.002	0.082-0.352
Baseline GH	−0.001	0.002	.658	−0.005 to 0.003
Baseline IGF-1 (ng/mL)	0.00008	0.000	.408	0.000-0.000
Radiological features				
Maximum tumor size	0.004	0.004	.288	−0.003 to 0.012
Cavernous sinus invasion	−0.087	0.076	.255	−0.237 to 0.063
Histopathological features				
PRL staining	0.005	0.072	.942	−0.138 to 0.148
Ki-67 Index	0.058	0.021	.007	0.016-0.100
Sparsely granulated adenoma	0.052	0.080	.513	−0.105 to 0.210
Treatments				
Postoperative remission	−0.188	0.076	.013	−0.338 to −0.039
SLAR use	−0.076	0.074	.309	−0.222 to 0.071
Cabergoline use	0.053	0.078	.494	−0.100 to 0.207
Pegvisomant use	0.011	0.109	.923	−0.204 to 0.226
Repeat TSS	0.002	0.090	.979	−0.175 to 0.179
Radiotherapy	0.007	0.093	.942	−0.177 to 0.190

B, unstandardized regression coefficient; CI, confidence interval; GH, growth hormone; IGF-1/ULN, insulin-like growth factor 1/upper limit of normal; PRL, prolactin; SLAR, somatostatin receptor ligand; TSS, transsphenoidal surgery.

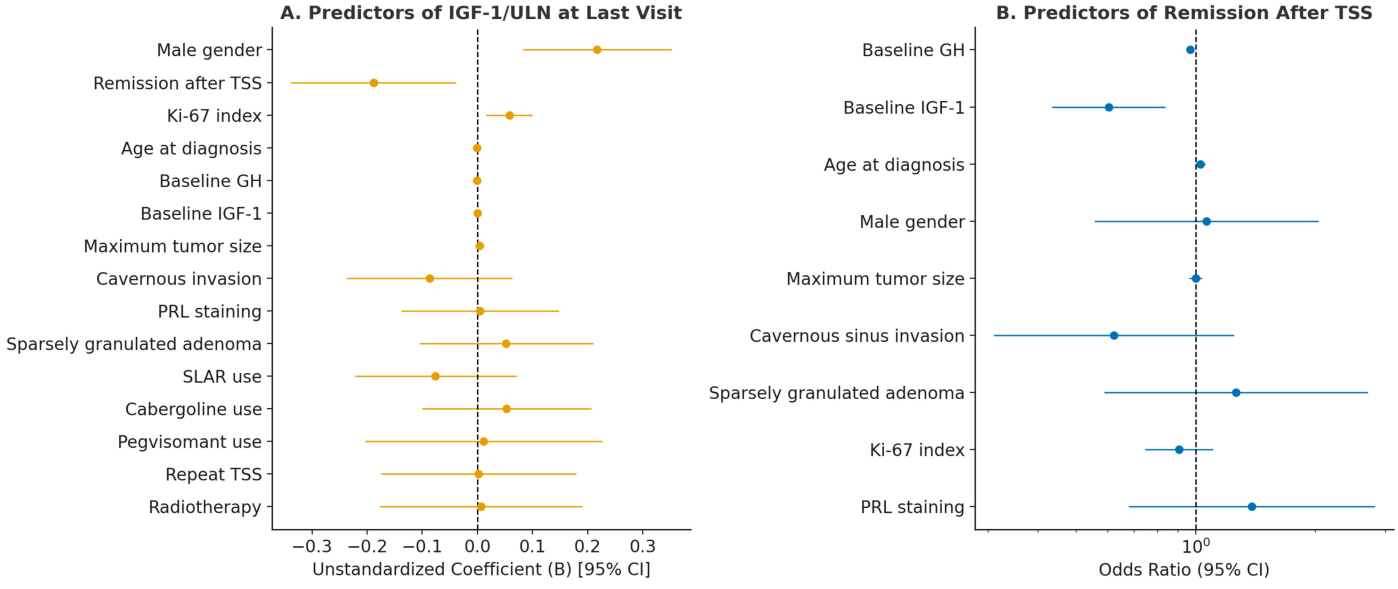


Figure 1.Forest plots showing the independent predictors of biochemical and surgical outcomes in patients with acromegaly. (A) Multivariable linear regression analysis for predictors of insulin-like growth factor 1/upper limit of normal at the last visit. (B) Multivariable logistic regression analysis for predictors of surgical remission after initial transsphenoidal surgery. GH, growth hormone; IGF-1, insulin-like growth factor 1; PRL, prolactin; SLAR, somatostatin receptor ligand; TSS, transsphenoidal surgery; ULN, upper limit of normal.

Table 4. Predictors of Surgical Remission

Predictor	Odds Ratio	95% CI for Odds Ratio	*P*
Baseline features			
Age at diagnosis	1.026	0.996-1.056	.090
Gender	1.063	0.555-2.037	.853
Baseline GH	0.968	0.946-0.991	.007
Baseline IGF-1	0.603	0.434-0.837	.002
Radiological features			
Maximum tumor size	0.998	0.961-1.036	.914
Cavernous sinus invasion	0.622	0.310-1.248	.181
Histopathological features			
Sparsely granulated adenoma	1.262	0.588-2.706	.550
Ki-67 index	0.907	0.745-1.106	.335
PRL staining	1.381	0.676-2.820	.376

GH, growth hormone; IGF-1, insulin-like growth factor-1; PRL, prolactin.

had lower GH levels than those with merely GH–secreting adenoma. Nevertheless, previous data were not entirely uniform. The recent ACRO-SPAIN cohort reported comparable GH concentrations between GH&PRL-PAs and GH-PAs, although IGF-1 was lower in the GH&PRL-PA group.[9] Rick et al[5] reported higher IGF-1 levels in GH- and PRL-staining tumors, whereas Lv et al,[6] using a more detailed pathological classification, found no significant baseline differences in nadir GH or IGF-1 among pure somatotroph, mammosomatotroph, and mixed somatotroph–lactotroph adenomas. These discrepancies probably reflect differences in tumor definitions, including serum PRL-based classification, immunohistochemical staining, and more refined pathological subtyping. Taken together, the results support the concept that PRL co-staining identifies a hormonally distinct subgroup of somatotroph tumors, although its impact on GH and IGF-1 secretion may vary according to the criteria used to define GH&PRL-PAs.

The reason for the lower GH levels observed in GH&PRL-PAs throughout the disease course remains unclear. One possible explanation is that GH secreted by these tumors may differ in its biological activity or peripheral sensitivity. Another possible explanation is the heterogeneous cellular composition of GH&PRL-PAs, particularly in mixed somatotroph–lactotroph tumors, in which not all tumor cells may contribute equally to GH production. This can result in lower measurable GH secretion. However, these hypotheses remain speculative and require further confirmation.

Most patients in this cohort presented with macroadenomas, which accounted for 78.5% of the study population. The maximum tumor diameter was comparable between GH&PRL-PAs and GH-PAs. Interestingly, cavernous sinus invasion was less frequent in GH&PRL-PAs than in GH-PAs. This finding suggested that pure GH-only pituitary adenomas have a more invasive radiological phenotype in the cohort. Regarding tumor size and radiological invasiveness, previous studies have reported inconsistent findings. Wang et al[4] found that patients with GH and PRL hypersecretion had larger adenomas than those with isolated GH–secreting tumors. Similarly, the ACRO-SPAIN cohort reported a higher prevalence of macroadenomas in GH&PRL-PAs and a trend toward more frequent cavernous sinus invasion.[9] In line with these findings, Biagetti et al[17] also observed a higher macroadenoma rate among GH&PRL-PAs in a cohort of treatment-naive patients receiving first-line medical therapy.

However, not all studies support a uniformly more invasive radiological phenotype. Rick et al[5], who classified tumors according to GH and PRL immunostaining, found similar tumor sizes and cavernous sinus invasion rates between dual-staining and single-staining somatotroph adenomas. Moreover, Lv et al[6] showed that radiological behavior may vary according to pathological subtype: mammosomatotroph adenomas tended to be smaller and less invasive, whereas mixed somatotroph–lactotroph adenomas showed a more aggressive radiological profile compared to pure GH–secreting pituitary adenomas. Therefore, the available literature suggests that the relationship between PRL co-expression and tumor size or invasiveness is not straightforward. In the authors' opinion, PRL co-staining alone may not be sufficient to define an invasive tumor phenotype, and other biological determinants should be taken into consideration.

Although lower GH levels at presentation can suggest a more favorable surgical and long-term prognosis in GH&PRL-PAs, this was not reflected in short- and long-term outcomes in the cohort. In this study, surgical remission and long-term biochemical control rates were similar between GH&PRL-PAs and GH-PAs. Previous studies have reported inconsistent results. Some series found comparable surgical remission and recurrence rates between GH&PRL-PAs and GH-PAs, whereas others reported lower remission rates, longer time to remission, and greater need for postoperative medical therapy in GH&PRL-PAs.[4-6,9,16,17] More detailed pathological classifications further suggest that outcomes may differ according to tumor subtype, with mammosomatotroph adenomas generally showing a more favorable profile and mixed somatotroph–lactotroph adenomas showing poorer long-term remission.[6]

Cavernous sinus invasion has been recognized as an important determinant of both surgical remission and long-term biochemical control in acromegaly.[18-23] Nevertheless, the lower frequency of cavernous sinus invasion observed in GH&PRL-PAs in this study did not lead to better outcomes. This finding may have been partly explained by the management of patients in an experienced pituitary center, where surgical expertise might have reduced the impact of adverse radiological features on outcomes.[24-26] In addition, effective postoperative management, including long-acting SLARs, cabergoline, and pegvisomant, as well as repeat TSS and radiotherapy in selected cases, may have contributed to comparable long-term biochemical control despite differences in cavernous sinus invasion.[18,27] It can be proposed that integrated multidisciplinary care and individualized postoperative treatment might have mitigated the prognostic impact of radiological invasiveness.

A central goal in the management of acromegaly is to achieve age-adjusted safe IGF-1 levels, as biochemical control is closely associated with reduced cardiovascular burden and improved long-term prognosis. Therefore, identifying the determinants of IGF-1 levels during follow-up has clear clinical relevance. In this study, female sex, a lower Ki-67 index, and achievement of surgical remission emerged as predictors of last-visit IGF-1 levels. Notably, none of these parameters differed significantly between GH&PRL-PAs and GH-PAs. Although some studies have linked PRL co-expression to poorer outcomes, its independent prognostic value for long-term remission remains unclear.[4-6,9,16,17] Available data suggest that tumor burden, invasiveness, and surgical success are more consistent determinants of long-term outcome than PRL staining alone. Although GH-only staining has been reported as an

independent predictor of surgical remission in 1 study,[5] the findings did not support this notion.

In the present study, a higher Ki-67 index was independently associated with higher last-visit IGF-1/ULN values, suggesting a possible relationship between tumor proliferative activity and long-term biochemical control. Ki-67 is a widely used marker of cellular proliferation in pituitary neuroendocrine tumors, and previous studies in GH–secreting pituitary adenomas have linked higher Ki-67 indices to poorer postoperative outcomes and reduced biochemical control during SLAR therapy.[28,29] Therefore, although Ki-67 should not be interpreted as a stand-alone prognostic marker, it may provide complementary information when assessing postoperative risk and planning follow-up intensity in patients with acromegaly.

This study has limitations. First, its retrospective design may have introduced inherent biases. Second, the classification was primarily based on GH and PRL immunostaining. However, GH&PRL-positive tumors may represent biologically distinct entities, including mammosomatotroph and mixed somatotroph–lactotroph tumors, which may differ in clinical behavior and prognosis. This study was not designed or sufficiently powered to distinguish these subtypes in detail. Therefore, future studies incorporating transcription factor profiling and refined pathological classification are needed to better define the prognostic relevance of PRL co-expression in acromegaly.

Growth hormone and prolactin co-staining pituitary adenomas comprised approximately one-third of patients with acromegaly in this large single-center cohort. Growth hormone and prolactin co-staining pituitary adenomas showed a distinct hormonal profile, with lower GH levels at presentation and throughout follow-up, but PRL co-staining itself was not an independent predictor of surgical remission or long-term biochemical control. Instead, long-term biochemical control was mainly associated with sex, Ki-67 index, and achievement of surgical remission. These findings suggest that PRL co-staining may define a pathologically distinct subgroup of somatotroph tumors, but its prognostic impact should be interpreted together with tumor-related and treatment-related factors rather than as an isolated marker.

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: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (Approval No.: 692023; Date: May 22, 2023).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.S., P.K.; Design – C.S., P.K.; Supervision – N.T., N.G., P.K.; Resources – C.S., C.T.S.; Materials – N.T., N.G.; Data Collection and/or Processing – C.S., P.K., C.T.S., N.G.; Analysis and/or Interpretation – C.S., C.T.S., P.K., N.G.; Literature Search – C.S., P.K., N.G.; Writing – C.S., N.G., P.K.; Critical Review – C.S.,, C.T.S., N.T., N.G., P.K.

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

Funding: The authors declare that this study received no financial support.

References

1. Sherlock M, Woods C, Sheppard MC. Medical therapy in acromegaly. *Nat Rev Endocrinol*. 2011;7(5):291-300. [CrossRef]
2. Guaraldi F, Ambrosi F, Ricci C, et al. Histopathology of growth hormone-secreting pituitary tumors: state of the art and new perspectives. *Best Pract Res Clin Endocrinol Metab*. 2024;38(3):101894. [CrossRef]
3. Asa SL, Mete O, Perry A, et al. Overview of the 2022 WHO classification of pituitary tumors. *Endocr Pathol*. 2022;33(1):6-26. [CrossRef]
4. Wang M, Mou C, Jiang M, et al. The characteristics of acromegalic patients with hyperprolactinemia and the differences in patients with merely GH-secreting adenomas: clinical analysis of 279 cases. *Eur J Endocrinol*. 2012;166(5):797-802. [CrossRef]
5. Rick J, Jahangiri A, Flanigan PM, et al. Growth hormone and prolactin-staining tumors causing acromegaly: a retrospective review of clinical presentations and surgical outcomes. *J Neurosurg*. 2019;131(1):147-153. [CrossRef]
6. Lv L, Jiang Y, Yin S, et al. Mammosomatotroph and mixed somatotroph-lactotroph adenoma in acromegaly: a retrospective study with long-term follow-up. *Endocrine*. 2019;66(2):310-318. [CrossRef]
7. Guo X, Zhang R, Zhang D, et al. Hyperprolactinemia and hypopituitarism in acromegaly and effect of pituitary surgery: long-term follow-up on 529 patients. *Front Endocrinol (Lausanne)*. 2021;12:807054. [CrossRef]
8. Araujo-Castro M, Marazuela M, Puig-Domingo M, et al. Prolactin and growth hormone signaling and interlink focused on the mammosomatotroph paradigm: a comprehensive review of the literature. *Int J Mol Sci*. 2023;24(18):14002. [CrossRef]
9. Araujo-Castro M, Biagetti B, Menéndez Torre E, et al. Differences between GH- and PRL-Cosecreting and GH-secreting pituitary adenomas: a series of 604 cases. *J Clin Endocrinol Metab*. 2024;109(12):e2178-e2187. [CrossRef]
10. Melmed S, Casanueva FF, Cavagnini F, et al. Guidelines for acromegaly management. *J Clin Endocrinol Metab*. 2002;87(9):4054-4058. [CrossRef]
11. Katznelson L, Laws ER, Jr, Melmed S, et al. Acromegaly: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951. [CrossRef]
12. Giustina A, Chanson P, Bronstein MD, et al. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab*. 2010;95(7):3141-3148. [CrossRef]
13. Giustina A, Biermasz N, Casanueva FF, et al. Consensus on criteria for acromegaly diagnosis and remission. *Pituitary*. 2024;27(1):7-22. [CrossRef]
14. Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab*. 2000;85(2):526-529. [CrossRef]
15. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(11):3888-3921. [CrossRef]
16. Varlamov EV, Wood MD, Netto JP, et al. Cystic appearance on magnetic resonance imaging in bihormonal growth hormone and prolactin tumors in acromegaly. *Pituitary*. 2020;23(6):672-680. [CrossRef]
17. Biagetti B, Araujo-Castro M, Torre EM, et al. Effectiveness of combined first-line medical treatment in acromegaly with prolactin cosecretion. *Eur J Endocrinol*. 2024;190(6):458-466. [CrossRef]
18. Sulu C, Onay G, Bakhdiyarli G, et al. Revisiting mortality in acromegaly using machine learning. *Endocrine*. 2025;90(3):1423-1437. [CrossRef]
19. Rutkowski M, Zada G. Management of pituitary adenomas invading the cavernous sinus. *Neurosurg Clin N Am*. 2019;30(4):445-455. [CrossRef]
20. Raverot G, Dantony E, Beauvy J, et al. Risk of recurrence in pituitary neuroendocrine tumors: a prospective study using a five-tiered classification. *J Clin Endocrinol Metab*. 2017;102(9):3368-3374. [CrossRef]
21. Micko ASG, Wöhrer A, Wolfsberger S, et al. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg*. 2015;122(4):803-811. [CrossRef]

22. Lefevre E, Chasseloup F, Hage M, et al. Clinical and therapeutic implications of cavernous sinus invasion in pituitary adenomas. *Endocrine*. 2024;85(3):1058-1065. [CrossRef]
23. Brochier S, Galland F, Kujas M, et al. Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. *Eur J Endocrinol*. 2010;163(2):193-200. [CrossRef]
24. Goyal-Honavar A, Sarkar S, Asha HS, et al. Impact of experience on outcomes after endoscopic transsphenoidal surgery for acromegaly. *World Neurosurg*. 2021;151:e1007-e1015. [CrossRef]
25. Gittoes NJL, Sheppard MC, Johnson AP, et al. Outcome of surgery for acromegaly—the experience of a dedicated pituitary surgeon. *QJM: Int J Med*. 1999;92(12):741-745. [CrossRef]
26. Colao A, Attanasio R, Pivonello R, et al. Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. *J Clin Endocrinol Metab*. 2006;91(1):85-92. [CrossRef]
27. Lim DST, Fleseriu M. The role of combination medical therapy in the treatment of acromegaly. *Pituitary*. 2017;20(1):136-148. [CrossRef]
28. Kasuki L, Wildemberg LEA, Neto LV, et al. Ki-67 is a predictor of acromegaly control with octreotide LAR independent of SSTR2 status and relates to cytokeratin pattern. *Eur J Endocrinol*. 2013;169(2):217-223. [CrossRef]
29. Fusco A, Zatelli MC, Bianchi A, et al. Prognostic significance of the Ki-67 labeling index in growth hormone-secreting pituitary adenomas. *J Clin Endocrinol Metab*. 2008;93(7):2746-2750. [CrossRef]