

First-week Postoperative Morning Serum Cortisol Nadir as a Potential Rule-Out Marker for Secondary Adrenal Insufficiency After Pituitary Surgery: A Retrospective Cohort Study

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Abstract

Purpose

We aimed to evaluate the diagnostic performance of morning serum cortisol nadir (MSCN), within the first week after pituitary surgery (PS), to exclude secondary adrenal insufficiency (SAI) at short- and mid-term postoperative follow-up.

Methods

We conducted a retrospective cohort study including adults undergoing transsphenoidal PS at a tertiary center, without Cushing's disease or unknown hypothalamic-pituitary-adrenal axis (HPAA) status. The lowest morning serum cortisol value within the first week after PS was recorded. SAI diagnosis at 1–3 months and 9–12 months was based on clinical judgment.

Results

We included 116 patients undergoing 129 PS. SAI was present in 30/112 (24%) and 23/112 (21%) 1–3 and 9–12 months, after PS, respectively. At 1–3 months, median early postoperative MSCN was 1.30 (IQR 0.67–3.73) in patients with SAI vs. 11.50 (8.14–15.40) $\mu\text{g/dL}$ in those with an intact HPAA ($p < 0.001$); at 9–12 months, 1.18 (0.60–3.60) vs. 10.90 (7.70–14.65) $\mu\text{g/dL}$, respectively ($p < 0.001$). The ROC curves showed an area under the curve of 0.967 and 0.888 for SAI at 1–3 and 9–12 months, respectively. A MSCN threshold of 6.7 $\mu\text{g/dL}$ (185 nmol/L) yielded sensitivities of 96.7% and 91.3%, specificities of 90.7% and 85.4%, and negative predictive values of 98.9% and 97.4% for predicting intact HPAA function at 1–3 and 9–12 months follow-up, respectively.

Conclusion

A MSCN $\geq 6.7 \mu\text{g/dL}$ within the first postoperative week reliably excludes SAI at both short- and mid-term follow-up. Following prospective validation, this threshold may support glucocorticoid replacement therapy before hospital discharge.

Introduction

Pituitary surgery is the treatment of choice for most symptomatic pituitary adenomas (excluding prolactinomas) and is generally safe when performed by an experienced neurosurgical team [1]. Despite the favorable safety profile of the endoscopic transsphenoidal approach, postoperative hypopituitarism remains an important complication. In particular, secondary adrenal insufficiency, which requires prompt recognition and intervention because of its potentially life-threatening nature [2–4].

At our institution, patients with an intact hypothalamic–pituitary–adrenal axis are not routinely treated with hydrocortisone in the perioperative period. Morning serum cortisol level is routinely assessed post-surgery, from day 1 to day 3; patients with a level lower than 10 µg/dL (276 nmol/L) are initiated on hydrocortisone replacement therapy until further assessment is performed at the outpatient clinic follow-up.

Because inappropriate glucocorticoid replacement may expose patients to avoidable adverse effects, numerous studies have investigated strategies to accurately predict postoperative secondary adrenal insufficiency. Although several studies have evaluated the predictive value of postoperative serum cortisol concentrations, the optimal cortisol threshold and timing of measurement remain uncertain, with considerable variability reported across the literature [5, 6].

The aim of this study was to evaluate whether the morning serum cortisol nadir within the first postoperative week may reliably exclude secondary adrenal insufficiency at short-term (1–3 months) and mid-term (9–12 months) following pituitary surgery.

Materials and Methods

Study design and population

A retrospective longitudinal cohort study was conducted at a tertiary center. All adults with a pituitary tumor who underwent partial or total endoscopic endonasal transsphenoidal resection were considered. Patients were excluded if they had a previous diagnosis of Cushing's disease or established preoperative secondary adrenal insufficiency, had been submitted to pituitary surgery by a different surgical team, lacked preoperative or postoperative morning serum cortisol measurements, had no follow-up data during the first postoperative year, or if the serum cortisol measurements used in the analysis had been performed using an analytical platform other than Abbott® ARCHITECT® or Roche® cobas®. For the analysis, patients were excluded if they underwent radiotherapy or further pituitary surgery during the first year after surgery. Patients receiving glucocorticoids for indications other than secondary adrenal insufficiency at the time of cortisol assessment were excluded from the corresponding analysis.

Data were collected from electronic medical records, ensuring complete anonymization. The following variables were analyzed: gender, age, morning serum cortisol value, tumor size, number and type of pituitary surgery, histopathological and immunohistochemistry diagnosis, and glucocorticoid treatment.

The study was reviewed and approved by the Hospital Administration Board and the Health Ethics Committee (project INV 899). The requirement for informed consent was waived because of the study's retrospective observational design, the absence of study-related interventions, and the use of anonymized data.

Surgical Procedure

All patients underwent endoscopic endonasal transsphenoidal surgery performed by the same pituitary surgical team, under general anesthesia and according to the same protocol. Following bilateral endonasal access, a posterior septostomy and sphenoidotomy were performed to expose the sellar region. The sellar floor was opened and the dura mater incised, allowing tumor resection. The extent of resection was determined by tumor characteristics and adjacent anatomical structures. In cases of intraoperative cerebrospinal fluid leakage, skull base reconstruction was performed using a multilayer closure technique, which could include dural substitutes, autologous grafts, vascularized nasoseptal flaps, and surgical sealants.

Hormonal assessment and perioperative management

Morning serum cortisol was measured during the first postoperative week using a chemiluminescence or electrochemiluminescence immunoassay. From October 2014 to June 2022 cortisol measurement was performed using the Abbott® ARCHITECT® assay (reference range 3.7 to 19.5 µg/dL); from July 2022 to December 2025, the Roche® cobas® assay (reference range 4.82 to 19.5 µg/dL) was used. Postoperative secondary adrenal insufficiency was suspected if a value lower than 10 µg/dL (276 nmol/L) was obtained. Patients were then treated with hydrocortisone until further assessment at the outpatient clinic. The lowest recorded value during this period was used for data analysis.

Outcomes

Secondary adrenal insufficiency was assessed at short-term (1–3 months) and mid-term (9–12 months) after pituitary surgery during scheduled endocrinology and/or neurosurgery outpatient follow-up. The diagnosis of secondary adrenal insufficiency was defined by the presence of compatible clinical symptoms and signs, supportive biochemical findings, and a clinical decision by the treating physician to initiate or continue glucocorticoid replacement. Dynamic confirmatory testing was not routinely performed and was reserved for patients in whom the combination of clinical and biochemical findings was insufficient to establish a definitive diagnosis.

Statistical analysis and reporting

IBM® SPSS Statistics® version 29 (Armonk, New York, United States of America) was used for statistical analysis. Continuous variables were presented as mean ± standard deviation or median (interquartile range) according to their normal or non-normal distribution, respectively. T-student and Mann-Whitney U tests were used to compare the means and the medians, respectively. Chi-square or Fisher's exact test were used to compare categorical variables. Receiver operating characteristic (ROC) curve analysis was used to assess diagnostic performance. Area under the curve (AUC), sensitivity, specificity, and negative predictive value were calculated. The cutoff was chosen based on clinical judgment. Boxplot analysis was used to identify outliers according to Tukey's rule. Secondary analyses for attrition bias and assay influence were also performed. Separate multivariable binary logistic

regression models were fitted, for each follow-up time point, with secondary adrenal insufficiency as the dependent variable. Each model included early postoperative cortisol and one additional covariate: gender, age, tumor size, and number of surgeries. A p value below 0.05 was considered statistically significant.

This study was reported in accordance with the STROBE statement and incorporated relevant STARD 2015 recommendations for diagnostic accuracy studies [7, 8].

Results

A total of 328 pituitary surgeries, performed between 1999 and 2025, were reviewed. Of these, 199 were excluded: 42 related to Cushing's disease, 63 with established preoperative secondary adrenal insufficiency, 15 submitted to surgery by a different surgical team, 22 without available preoperative cortisol levels, 54 without available follow-up data, and 3 due to measurement with a different cortisol assay (Beckman Coulter®; reference range 6.7 to 22.6 µg/dL). Therefore, 129 surgeries, relating to 116 patients, performed between 2014 and 2025 were included (Fig. 1).

Baseline demographic, surgical and pathological characteristics are summarized in Table 1. Most lesions were pituitary neuroendocrine tumors (Pit-NET), also known as pituitary adenomas (111/129 surgeries, 86%).

Table 1
Baseline characteristics per surgery (total patients: 116).

Characteristics	n (%)
Total surgeries	129
Male	64 (50)
Female	65 (50)
Mean age (years; mean $\pm$ SD)	57 $\pm$ 14
Surgery	
First	105 (81)
Second	20 (16)
Third	2 (2)
Fourth	2 (2)
Tumor size (mm; mean $\pm$ SD)	24 $\pm$ 12
Preoperative cortisol (μ g/dL; mean $\pm$ SD)	12.48 $\pm$ 4.38
Histopathological diagnosis	
Pituitary adenoma	111 (86)
Gonadotroph	39 (35)
Somatotroph	23 (21)
Lactotroph	4 (4)
Plurihormonal	22 (20)
Hormone-negative without transcription factor analysis ^a	19 (17)
Immunohistochemistry unavailable	4 (4)
Craniopharyngioma	4 (3)
Meningioma	4 (3)
Rathke's cleft cyst	3 (2)
Arachnoid cyst	2 (1)

SD – standard deviation. ^aHormone-negative adenomas without transcription factor analysis were negative for pituitary hormone immunostaining but were not evaluated for PIT1, T-PIT, or SF1 expression, precluding definitive lineage classification. ^bBoth cases were reoperations of mixed GH and PRL secreting pituitary adenoma with no tumor specimen found at the retrieved tissue. ^cOther lesions included one suprasellar epidermoid cyst, one sellar cyst, and one xanthogranuloma associated with a Rathke's cleft cyst.

Characteristics	n (%)
Normal adenohypophyseal tissue ^b	2 (1)
Other sellar/suprasellar lesions ^c	3 (2)
SD – standard deviation. ^a Hormone-negative adenomas without transcription factor analysis were negative for pituitary hormone immunostaining but were not evaluated for PIT1, T-PIT, or SF1 expression, precluding definitive lineage classification. ^b Both cases were reoperations of mixed GH and PRL secreting pituitary adenoma with no tumor specimen found at the retrieved tissue. ^c Other lesions included one suprasellar epidermoid cyst, one sellar cyst, and one xanthogranuloma associated with a Rathke's cleft cyst.	

Median first week postoperative minimum morning serum cortisol was 9.90 (5.25–14.15) µg/dL. Cortisol nadir occurred at a median of 2 (1–5) days after pituitary surgery. Mean postoperative cortisol measurements per pituitary surgery were 2.7 ± 1.0 measurements.

Secondary adrenal insufficiency was present in 30/127 (24%) procedures, 1–3 months after transsphenoidal surgery. Median early postoperative morning serum cortisol nadir was 1.30 (0.67–3.73) vs. 11.50 (8.14–15.40) µg/dL ($p < 0.001$) in secondary adrenal insufficiency vs. intact hypothalamic–pituitary–adrenal axis cases at this short-term follow-up (Fig. 2A). At mid-term follow-up (9–12 months after pituitary surgery), 23/112 (21%) cases were diagnosed with secondary adrenal insufficiency. Median early postoperative morning serum cortisol nadir was 1.18 (0.60–3.60) vs. 10.90 (7.70–14.65) µg/dL ($p < 0.001$) for those diagnosed with secondary adrenal insufficiency and those with intact hypothalamic–pituitary–adrenal axis, respectively. (Fig. 2B).

The ROC curves showed an AUC of 0.967 (95% CI 0.938–0.996) and 0.888 (95% CI 0.785–0.992) for secondary adrenal insufficiency at short- and mid-term follow-up, respectively (Figs. 3). A cutoff of 6.665 µg/dL (184 nmol/L) yielded a sensitivity of 96.7% and 91.3%, a specificity of 90.7% and 85.4%, and a negative predictive value of 98.9% and 97.4% at each time point. For ease of clinical application, this threshold may be rounded to 6.7 µg/dL (185 nmol/L), without affecting diagnostic performance in the present cohort.

Using this cutoff, only 1/89 patients would be discharged without hydrocortisone and diagnosed with secondary adrenal insufficiency 1–3 months later. This patient had a cortisol value of 8.98 µg/dL, was treated with hydrocortisone, and had a morning serum cortisol of 16.72 µg/dL (461 nmol/L) one month after pituitary surgery. However, as interference by hydrocortisone intake could not be excluded, secondary adrenal insufficiency was not ruled out. At the 9–12 months appointment, secondary adrenal insufficiency was excluded.

Among the 78 patients who would have been discharged without hydrocortisone based on the same cutoff, two were diagnosed with secondary adrenal insufficiency 9–12 months later. These patients had an early postoperative minimum morning serum cortisol of 17 µg/dL (467 nmol/L) and 38.50 µg/dL (1062 nmol/L), with no suspected laboratory interference and no clinical indication for hydrocortisone

treatment. The first patient probably developed secondary adrenal insufficiency after 3 months of follow-up, with no specific cause identified. The second patient was treated with dexamethasone for six weeks due to the development of psychomotor lentification in the context of major surgical trauma (she was excluded from the first time-point analysis due to clear laboratory interference). Treatment was then switched to hydrocortisone. At 9–12 months after pituitary surgery, morning cortisol was 12.9 µg/dL, but interference by hydrocortisone treatment could not be excluded and secondary adrenal insufficiency was assumed. Further assessment showed appropriate recovery of the hypothalamic–pituitary–adrenal axis.

Six extreme cortisol values were identified by boxplot analysis, ranging from 33.3 to 57.1 µg/dL. A thorough review showed clinical plausibility and absence of glucocorticoid treatment interference. Therefore, sensitivity analysis was not performed.

At the short-term follow-up analysis, only 127 cases were included. One patient did not attend the outpatient follow-up appointment between 1 and 3 months, and another was under dexamethasone treatment, as previously described. At the mid-term follow-up analysis, 17 patients were excluded: 9 were lost to follow-up, 4 were submitted to surgery less than 9 months before the end of the study, 2 were resubmitted to surgery between 1–3 months and 9–12 months after initial surgery, one was submitted to radiosurgery, and one was started on prednisolone regimen for an autoimmune disease. Supplementary Table 1 shows the comparison of baseline characteristics, early postoperative morning serum cortisol nadir and secondary adrenal insufficiency diagnosis 1–3 months after surgery, between patients included and excluded from this study analysis. No significant difference was found between the two groups. There was also no difference in early postoperative morning serum cortisol nadir, whether the measurement was made using the Roche® or Abbott® assays ($p = 0.933$).

In the multivariable analyses, higher early postoperative morning serum cortisol nadir remained a clear predictor of secondary adrenal insufficiency at both 1–3 months (OR 0.503, 95% CI 0.388–0.651; $p < 0.001$) and 9–12 months (OR 0.766, 95% CI 0.677–0.867; $p < 0.001$). After adjustment for early postoperative cortisol, a lower number of surgeries was associated with secondary adrenal insufficiency at 1–3 months (OR 0.040, 95% CI 0.003–0.517; $p = 0.014$), whereas greater tumor size was associated with secondary adrenal insufficiency at 9–12 months (OR 1.058, 95% CI 1.001–1.118; $p = 0.045$) (Table 2).

Table 2

Logistic regression models adjusted for early postoperative minimum morning serum cortisol for the risk of secondary adrenal insufficiency 1–3 and 9–12 months after pituitary surgery.

Variable	1–3 Months after surgery			9–12 Months after surgery		
	OR	95% CI	p value	OR	95% CI	p value
Early postoperative morning serum cortisol nadir ^a	0.503	0.388–0.651	< 0.001*	0.766	0.677–0.867	< 0.001*
Gender ^b	0.484	0.099–2.374	0.371	1.121	0.384–3.275	0.835
Age ^b	1.038	0.983–1.095	0.179	1.010	0.970–1.052	0.631
Tumor size ^b	1.057	0.976–1.146	0.174	1.058	1.001–1.118	0.045*
Number of surgeries ^b	0.040	0.003–0.517	0.014*	0.684	0.169–2.767	0.594
OR – odds ratio. CI – confidence interval. ^a Univariable analysis. ^b Multivariable analysis with cortisol. *Statistically significant.						
Supplementary Table 1. Comparison of cases retained and excluded in the analysis at 9–12 months according to baseline characteristics, early postoperative minimum morning serum cortisol, and secondary adrenal insufficiency at 1–3 months after surgery.						

Discussion

In our institution, patients with preoperative evidence of an intact hypothalamic–pituitary–adrenal axis are not routinely treated with hydrocortisone in the perioperative period. Following Inder et al. guidelines, morning serum cortisol level is assessed from day 1 to day 3 post-surgery, and patients with any value lower than 10 µg/dL (276 nmol/L) are treated with hydrocortisone until further assessment at the outpatient clinic [9]. However, this approach has not been validated in our center. Furthermore, several authors report a potential benefit of multiple cortisol measurements, mitigating the impact of gland manipulation, surgical trauma, and general anesthesia on cortisol levels in the early postoperative days [5, 9, 10]. To facilitate interpretation and implementation, we used the morning serum cortisol nadir within the first week after pituitary surgery and assessed its predictive value for the development of secondary adrenal insufficiency at short- and mid-term periods following pituitary surgery.

We included a well-characterized cohort of 116 patients who underwent a total of 129 transsphenoidal surgeries over a study period of more than a decade, submitted to pituitary surgery by the same experienced surgical team, and with follow-up data available at both 1–3 months and 9–12 months after surgery. Mean early postoperative cortisol measurements per pituitary surgery were 2.7 ± 1.0 measurements with its nadir occurring at a median of 2 (1–5) days after surgery.

Early postoperative morning serum cortisol nadir demonstrated a strong performance as a rule-out marker for secondary adrenal insufficiency. A cutoff of 6.7 µg/dL (185 nmol/L) yielded a sensitivity of 96.7% and 91.3%, a specificity of 90.7% and 85.4%, and a negative predictive value of 98.9% and 97.4% for the development of secondary adrenal insufficiency at short- and mid-term follow-up after pituitary surgery, respectively. The recommendation to use a postoperative cortisol threshold of 6.7 µg/dL (185 nmol/L) may therefore reduce unnecessary hydrocortisone treatment.

In multivariable analysis, larger tumor size was independently associated with higher odds of secondary adrenal insufficiency development at mid-term period after pituitary surgery (OR 1.058, 95% CI 1.001–1.118). This finding is consistent with that of Staby et al. [11], whereas other studies did not identify a significant association [5, 10]. At short-term period, however, the number of surgeries was inversely associated with secondary adrenal insufficiency development (OR 0.040, 95% CI 0.003–0.517), indicating higher odds of that outcome among patients with fewer surgeries. This direction contrasts with the unadjusted findings of Staby et al., who reported new secondary adrenal insufficiency in 44% (4/9) of previously operated patients compared with 5% (4/73) of surgery-naïve patients [11]. This discrepancy should be interpreted cautiously because repeated surgeries were relatively uncommon in both cohorts, resulting in markedly unbalanced groups and potentially unstable estimates, as reflected by the wide confidence interval in our analysis.

Some limitations should be considered before translating these findings into routine clinical practice. Firstly, confirmatory dynamic testing was not systematically performed. As a result, partial forms of secondary adrenal insufficiency may have been missed, potentially leading to an overestimation of diagnostic performance. Secondly, postoperative cortisol measurements guided clinical decisions regarding glucocorticoid replacement, and these treatment decisions were subsequently incorporated into the outcome assessment. Accordingly, incorporation bias cannot be completely excluded. Nevertheless, this approach reflects routine clinical practice, in which postoperative adrenal function is commonly evaluated through a combination of biochemical measurements, clinical assessment, and therapeutic decision-making, rather than systematic dynamic testing.

Previous studies using dynamic tests for confirmation have suggested higher cutoffs for morning cortisol measured by electrochemiluminescence and chemiluminescence immunoassays: 11.78–15.6 µg/dL (325–430 nmol/L) for safe exclusion of secondary adrenal insufficiency after pituitary surgery [5, 6, 11–13]. However, the primary objective of this study was not to establish a definitive diagnosis of secondary adrenal insufficiency using a dynamic test, but rather to identify a postoperative cortisol threshold associated with a low likelihood of clinically significant secondary adrenal insufficiency. Patients with borderline results may still benefit from a conservative approach with clear stress-dose glucocorticoid instructions and subsequent reassessment of the hypothalamic–pituitary–adrenal axis functionality. This approach is further supported by McLaughlin et al. who reported a cutoff of 4 µg/dL (110 nmol/L) on postoperative days 1 and 2 to safely exclude secondary adrenal insufficiency, reserving dynamic testing for patients with subnormal cortisol levels or clinical manifestations of secondary adrenal insufficiency [10].

The results may have also been influenced by the use of two assays for cortisol measurement. However, the two assays presented similar reference intervals and showed no significant difference in early postoperative morning serum cortisol nadir.

Another limitation is the potential interference of glucocorticoids on serum cortisol levels. We believe this limitation was mitigated by excluding patients without preoperative confirmation of an intact hypothalamic–pituitary–adrenal axis, and Cushing’s disease, who are routinely treated with hydrocortisone in the perioperative period. Additionally, the use of multiple values increases the diagnostic performance of the test [5, 10].

The exclusion of 17/129 cases from the mid-term analysis due to incomplete follow-up may reflect an attrition bias. Although no differences were found between the two groups regarding baseline characteristics, postoperative cortisol, and secondary adrenal insufficiency diagnosis at short-term period after surgery, differences in unknown variables may have influenced the results.

In addition, no internal or external validation has been carried out. Prospective validation in independent cohorts is warranted before widespread implementation.

In conclusion, a morning serum cortisol nadir of 6.7 µg/dL (185 nmol/L) obtained within the first week after transsphenoidal surgery showed a strong rule-out performance for secondary adrenal insufficiency, with a high negative predictive value maintained up to 12 months after surgery. As an inexpensive and widely available biomarker, it may support personalized postoperative glucocorticoid replacement strategies in patients with an intact hypothalamic–pituitary–adrenal axis.

Declarations

Funding

None of the authors have anything to disclose.

Author Contribution

All authors contributed to the study conception and design. Data collection was performed by J.O.T., A.F.B., J.B.C., and M.S.S.. Statistical analysis was performed by J.O.T.. The first draft of the manuscript was written by J.O.T., and all authors reviewed the manuscript.

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Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

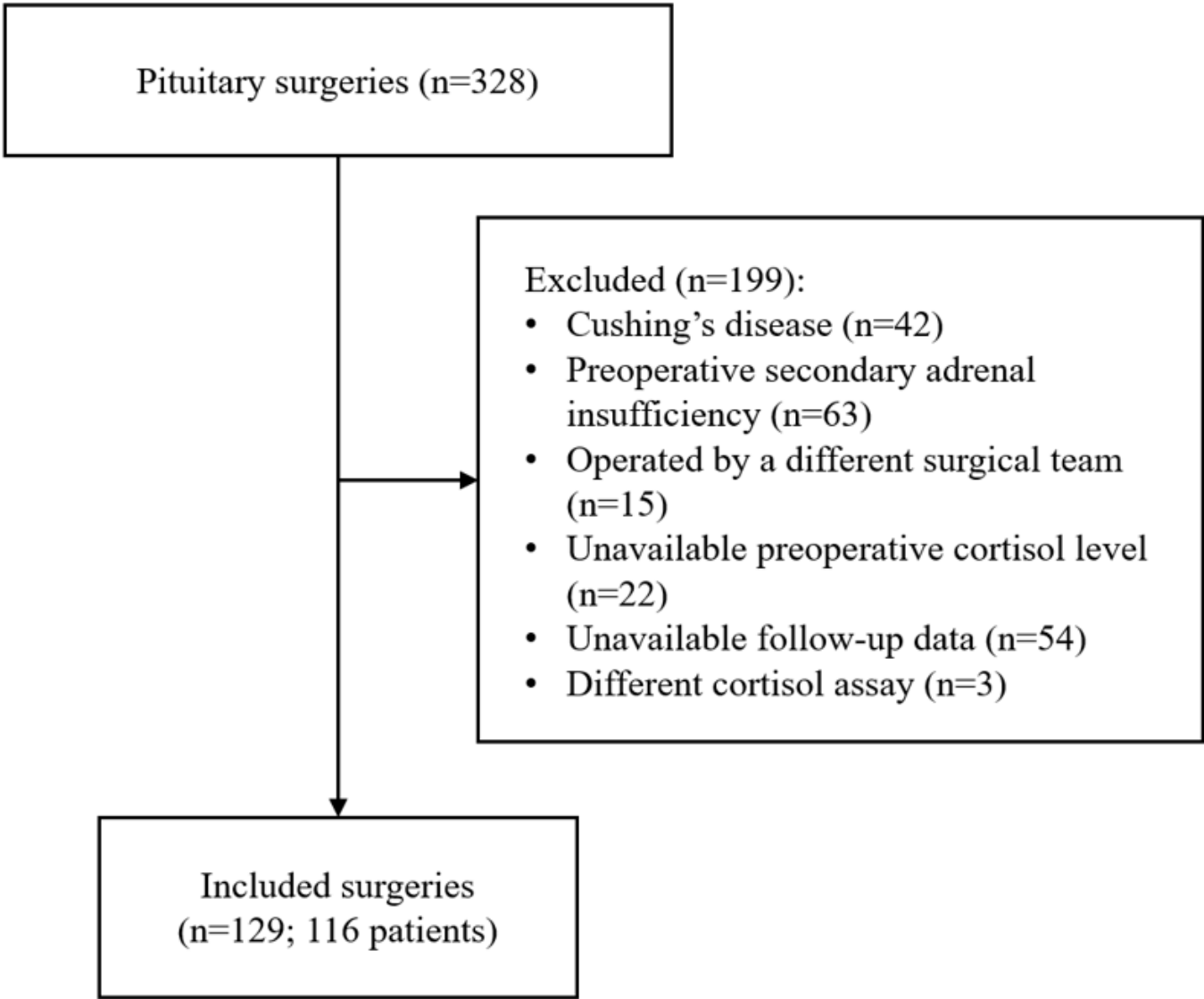


Figure 1

Study flowchart. Flow diagram illustrating the application of inclusion and exclusion criteria, and the final cohort included in the analysis.

Figure 2a

Figure 2b

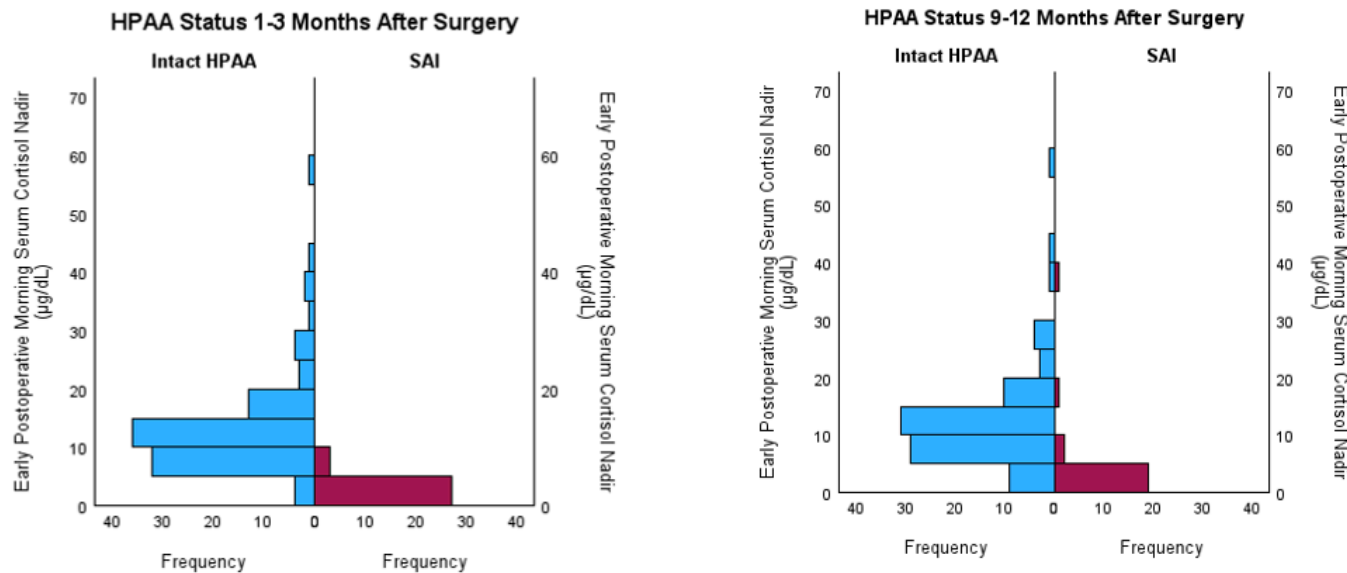


Figure 2

Distribution of early postoperative minimum morning serum cortisol concentration according to hypothalamic–pituitary–adrenal axis (HPAA) status after transsphenoidal surgery. (a) At 1–3 months, hypothalamic–pituitary–adrenal axis function was intact in 97/127 surgical episodes (76%), with a median cortisol concentration of 11.50 µg/dL (IQR 8.14–15.40), while secondary adrenal insufficiency was present in 30/127 episodes (24%), with a median cortisol concentration of 1.30 µg/dL (IQR 0.67–3.73). (b) At 9–12 months, hypothalamic–pituitary–adrenal axis function was intact in 89/112 surgical episodes (79%), with a median cortisol concentration of 10.90 µg/dL (IQR 7.70–14.65), while secondary adrenal insufficiency was present in 23/112 episodes (21%), with a median cortisol concentration of 1.18 µg/dL (IQR 0.60–3.60). Cortisol distributions differed significantly between groups at both time points (both p values <0.001).

Figure 3a

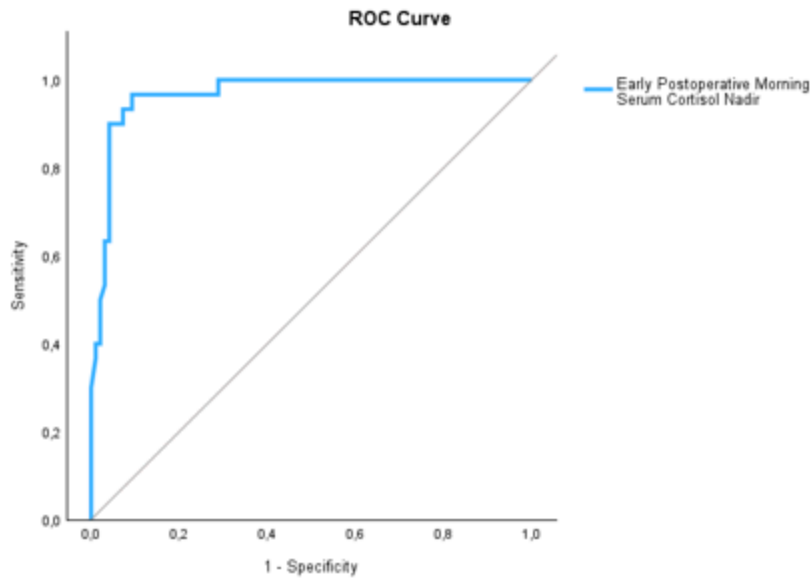


Figure 3b

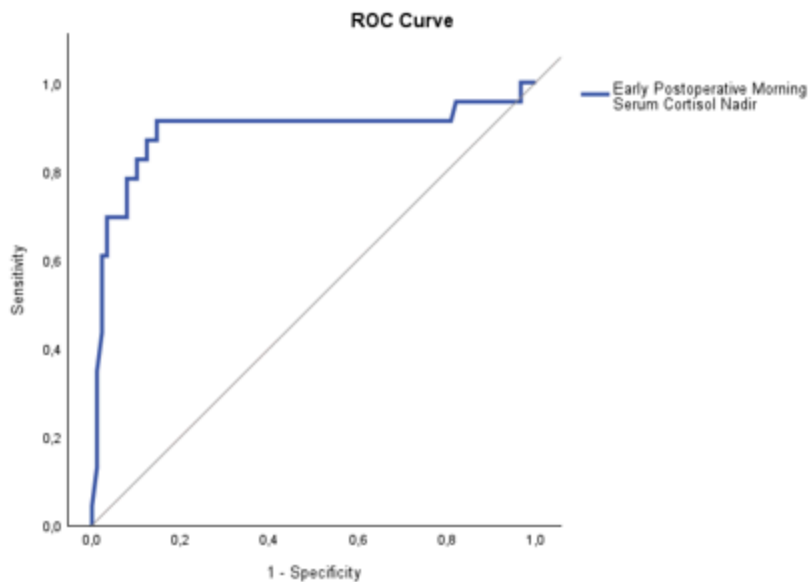


Figure 3

Receiver operating characteristic (ROC) curves of the early postoperative morning serum cortisol nadir concentration for predicting secondary adrenal insufficiency after transsphenoidal surgery. (a) At 1–3 months, the area under the curve (AUC) was 0.967 (95% CI 0.938–0.996). A cutoff of 6.665 $\mu\text{g/dL}$ (184 nmol/L) yielded a sensitivity of 96.7%, a specificity of 90.7%, and a negative predictive value (NPV) of 98.9%. (b) At 9–12 months, the AUC was 0.888 (95% CI 0.785–0.992). The same cutoff yielded a sensitivity of 91.3%, a specificity of 85.4%, and an NPV of 97.4%. Cortisol concentrations below the cutoff were considered positive for secondary adrenal insufficiency.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)