

Transsphenoidal Pituitary Adenoma Resection: Do Early Post-Operative Cortisol Levels Predict Permanent Long-Term Hormone Deficiency?

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Abstract

Objective: Transsphenoidal surgery provides a minimal invasive treatment for pituitary adenoma. Our aim is to evaluate the endocrinological outcomes after adenoma resection, and to identify prognostic factors for an impaired hypothalamic-pituitary-adrenal-axis function (HPA) and the reliability of postoperative early morning serum cortisol measurements.

Methods: Retrospective analysis of all patients treated for pituitary adenoma from April 2006 to January 2019 in our neurosurgical department. Pituitary function was assessed pre- and postoperatively as well as at 6 weeks to 12 weeks and at 1-year follow-up.

Results: 211 patients were included. 9% of the patients recovered from a preoperative adrenal insufficiency, 10.4% developed a new need for hormone substitution, and a long-term deficiency of the hypothalamic-pituitary-adrenal-axis was observed in 30.9%. Cortisol measurements 5 days after surgery had a lower area under the curve (AUC) than cortisol levels detected after 6 to 12 weeks (AUC 0.740 vs. AUC 0.808) in predicting a secondary adrenal insufficiency. The cut-off value determined for cortisol measured after 6 weeks was 6.95 µg/dl (sensitivity of 94%, specificity of 68%).

Conclusion: Postoperative early morning cortisol levels seem to be less sensitive and specific in predicting long-term hormone deficiency than measurements after 6 weeks and 1 year, emphasizing the importance of endocrine follow-up testing.

Introduction

Tumors of the pituitary gland account for approximately 15% of all intracranial tumors and the benign pituitary adenoma represent the most common encountered entity (up to 85%) [37,7,33,36] of all sellar lesions. The transnasal transsphenoidal (TSS) operative re-section of sella tumors has firstly been described in 1907 by Schlofer et al. and further developed by Cushing et al. in 1909 [23,5,34]. Nowadays, TSS is considered the most appropriate and initial approach for treatment of tumors of the pituitary gland [34,35]. It can reduce hospital costs by shortening the length of hospital stay (LOH) and presents a safe and effective surgical resection option with fewer complications and better clinical out-comes than the transcranial route [38,39].

Pituitary adenoma patients may present with mass effect and lead to a compression of the optic chiasm with visual field defects and impaired visual acuity. As the pituitary gland plays a pivotal role in hormone regulation, adenomas can lead to an impaired adrenal pituitary function or hormone hypersecretion such as Acromegaly or M. Cushing due to a hypersecretion of growth hormone (GH) or adrenocorticotrophic hormone (ACTH).

Most important is the preservation of an intact hypothalamic-pituitary-adrenal-axis (HPA) regulating in a circadian rhythm and depending on physical stress levels cortisol release through the stimulation of ACTH [12]. Therefore, patients need to be monitored closely for symptoms of hypocortisolism, the most

dangerous and life-threatening complication of pituitary deficiency [24], presenting with impaired metabolism such as anorexia, fatigue, hypotension and nausea and potentially leading to the lethal adrenal crisis including shock and volume depletion called Addison's crisis [29,15]. Many studies have focused on the optimal serum cortisol threshold (or cut-off value) to determine whether a patient suffers from hypocortisolism or not, and to prevent patients from adrenal corticotrophic deficiency by substituting hydrocortisone [37,26,27,14,3]. Minimum values range from 4 to 20 µg/dl (morning serum level, 1 µg/dl = 27,59 nmol/l), but only few conducted studies have been performed and published with a long enough follow-up to establish cortisol supplementation criteria [37,24,20].

The optimal cut-off value of morning fasting cortisol level plays a pivotal role in determining the risk for an anterior pituitary deficiency and needs to be detected early in order to start the optimal treatment, but also to avoid hydrocortisone over-replacement to minimize possible side effects like osteoporosis and impaired glucose tolerance [2]. Regular follow-up testing of the fasting morning cortisol levels is therefore performed before and after surgery, as well as at neurooncological follow-up appointments.

In our study, we focus on the diagnostic value of direct postoperative cortisol measurements and possible influencing prognostic factors to detect pituitary corticotrophic deficiency, in order to provide a reliable timing and cortisol cut-off value to predict long-term need of hydrocortisone replacement therapy.

Methods

We retrospectively analyzed all patients treated via TSS for histologically proven pituitary adenomas from April 2006 to January 2019 in our neurosurgical department in a tertiary referral hospital by two senior attending neurosurgeons.

Inclusion criteria were diagnosed hormone-inactive adenoma of the sella region, complete data available including complete clinical and endocrinological data such as cortisol serum levels, age > 18 years, minimum endocrinological and clinical follow-up of 1 year after surgery, surgery performed via a transsphenoidal approach. Patients with other tumors than adenoma of the sella region were excluded from our study. Patients presenting with pituitary apoplexy were included if complete endocrinological testing was performed before surgery and adenoma tissue was identified in the specimens sent to histopathology.

We retrieved demographic factors from our archives such as gender, age, Karnofsky performance scale (KPS), as well as comorbidities from patient files (preoperative ingestion of hydrocortisone due to rheumatoid arthritis or other autoimmune diseases), pre- and postoperative imaging (magnetic resonance imaging MRI, computed tomography CT) for extent of resection (gross total resection GTR vs. partial resection (PR)) and perioperative hormone levels of basal cortisol (µg/dl) gained from the patient in the morning (serum values, cobas 8000 analyzer Roche)). In cases of performed preliminary ACTH stimulation testing, we added the values to our data sheet. Urinary free cortisol levels were not included for analysis. Information on the operation performed included: microscopic vs. endoscopic approach, length of operation (mean time in minutes), and intra-operative complications (cerebrospinal fluid CSF

leak, major bleeding). The minimum clinical and endocrinological follow-up time was 1 year, and patients were monitored for anterior and posterior pituitary deficiency and need for hormone substitution after TSS. Corticotrophic hormone deficiency was also diagnosed when the patient presented with symptoms of hypocortisolism after withdrawing or reducing the hydrocortisone substitution, even if the basal morning serum cortisol level was above a defined threshold.

Statistical correlation analyzes were performed using the IBM SPSS software (Version 26.0.0.0). Multivariate analyzes were conducted to control for possible confounders. Cut-off values were determined using the Receiver-Operator Curve (ROC), area under the curve (AUC) and the Youden-Index [40]. Correlation analysis was performed using the Spearman coefficient, a p-value <0.05 was considered significant.

The presented study meets the ethical standards outlined in the Declaration of Helsinki, ethics approval was obtained before performing the analysis (Ethikkommission der Technischen Universität München, Prof. Dr. Schmidt) and the positive vote was registered under the number 231/20-S. Due to the retrospective nature of the study, in-formed consent was waived in accordance with the Ethics Commission. All methods were carried out in accordance with relevant guidelines and regulations.

Results

Patient population

We were able to identify 429 patients who were treated via the transsphenoidal approach for tumors of the sellar and parasellar region from April 2006 to January 2019 in our clinical neurosurgical department. 62 patients with hormone-producing adenoma causing Acromegaly and M. Cushing were excluded due to their distinct preoperative cortisol levels (Figure 1). 59 patients were excluded due to histopathological diagnosis of tumors other than pituitary adenoma (meningioma, Rathke's cleft cysts, hypophysitis) due to their distinct clinical outcome. 97 patients were lost to follow-up endocrinological data at 1 year.

In total, 211 patients were included for further analysis. Comparing the numbers over the years, we observed a trend towards increasing numbers of surgeries performed for transnasal pituitary adenoma resection (number of cases included between 2006-2012: n= 72, 2013-2019: 139 cases).

Median age was 56 years with a range of 20-86 years. 60% (n= 127) were male and 40% (n= 84) female patients. Median preoperative KPS was 90% (range 20-100%). 97.6% of the patients suffered from pituitary macroadenoma, only 5 patients presented with progressive hormone-inactive pituitary microadenoma (only selected cases such as patients presenting with tumor growth on follow-up imaging leading to the indication of surgical removal (2.4%)).

Hormone levels

All patients were given intra and postoperative hydrocortisone substitution according to the following standard scheme: patients obtained 50mg of intravenous hydrocortisone injection on induction, followed

by immediate initiation of a continuous infusion of hydrocortisone 100 mg/24h. On postoperative day 1, patients obtained 80mg (infusion for 24h). On day 2 after surgery, we continued with an oral administration of 60mg hydrocortisone (20mg in the morning, noon and evening) with continuous reduction of 10mg per day until the maintenance dosage of 20mg per day (10 mg in the morning and at noon).

Table 1 describes the preoperative values, postoperative values and long-term cortisol results after one year of patients grouped by corticotrophic deficiency. Mean pre-operative early morning cortisol level was 11.7 µg/dl (range 0.2 to 37.1 µg/dl) and mean postoperative (5 days after TSS) level was 12.6 µg/dl (range 0.2 to 45.1 µg/dl). At 6 weeks to 12 weeks, mean early morning cortisol level was 11.9 µg/dl (range 0.1 to 59.8 µg/dl) and long-term data (minimum 1-year follow-up) revealed a mean basal cortisol level of 11.2 µg/dl (range 0.1- 35.1 µg/dl).

If grouped by preoperative hormone corticotrophic deficiencies (with clinical cortico-tropic deficiency symptoms and need for hydrocortisone substitution), mean basal serum cortisol values in patients with corticotrophic hormone deficiency were 3.99 µg/dl and 15.1µg/dl. Mean hormone levels of basal cortisol at long-term follow-up (minimum 1 year) were 6.01 µg/dl for patients with long-term need of hydrocortisone substitution and 13.7 µg/dl for the healthy counterpart without replacement therapy (Figure 2 and 3, Table 1).

Clinical and surgical outcome

The overall clinical outcome showed satisfying postoperative results. Median postoperative KPS of our patients was 90% (range 40-100%). Mean duration of surgery was 84 minutes, ranging from 24 to 489 minutes. Of all performed surgeries, 68.1% of the TSS were performed with a microscope, and in 31.9% of the cases with an 0° or 30° endoscope. We did not identify any significant differences in terms of complications or clinical out-come between patients operated with the endoscope or microscopical approach.

Overall, perioperative complications occurred in 18% of the operated cases (occurrence of transient diabetes insipidus with the need for desmopressin substitution in 7.1%, occurrence of an intraoperative dural tear with the need for postoperative surgical revision in 4.7%, operative revision due to postoperative hemorrhage in only 3 cases 1.4%).

GTR was achieved in 79.1% (evaluated by analyzing the postoperative imaging and determined as no residual tumor detected on the postoperative MRI). Patients with residual (mostly suprasellar) tumor were advised to perform a follow-up MRI after 6-12 weeks. In cases with good access to the descended residual tumor, the patients underwent a second transnasal surgery.

Cut-off values, sensitivity and specificity

According to the Receiver Operator Characteristic (ROC) curves, cortisol levels analyzed 6 weeks to 3 months after surgery were more accurate in predicting long-term corticotrophic deficiency (Area Under the

Curve AUC 0.808) compared to the directly postoperative assessed levels (AUC 0.740). Naturally, the AUC of long-term basal cortisol levels predicted the hormone deficiency most appropriately (AUC 0.864) (Figure 4).

The cut-off value for direct postoperative basal cortisol level was 6.9 µg/dl (sensitivity 86.4%, specificity 56%, Youden-Index 0.424). For values measured after 6 to 12 weeks after surgery, the cut-off prognostic basal cortisol was 6.95 µg/dl with a sensibility of 94.1% and specificity of 68% (Youden-Index 0.621). Basal cortisol measured after at least one year after surgery had the highest prognostic power at a value of 8.35 µg/dl (sensitivity 90%, specificity 82%, Youden-Index 0.718) (Table 2).

Long-term hormone deficiency

Long-term hydrocortisone replacement after 1 year was observed in 30.9% of the patients and in 30.4% of the patients before surgical treatment. Overall, 9% recovered from a preoperative hormone deficiency of the HPA-axis, and 10.4% developed a new postoperative impaired HPA-axis leading to a corticotropic deficiency. In total, 80.6% of our patients had no changes regarding the pituitary function (persistent corticotropic deficiency without recovery or intact function postoperatively in patients without pre-operative corticotropic deficiency).

In 14.6%, the postoperative cortisol level was above the measured threshold of 6.9 µg/dl while patients still suffered from long-term hormone deficiency (false negative patients). False positive results occurred in 11.1% of the cases with our assessed direct postoperative cortisol cut-off value of 6.9 µg/dl (unnecessary hydrocortisone substitution in patients with intact HPA-axis). In total, regarding that all patients had a hydrocortisone replacement for safety reasons until the first endocrinological follow-up 6 weeks to 3 months after surgery, 66.3% of the patients underwent substitution while having a basal postoperative cortisol level above the determined threshold.

Prognostic factors

Gender, age, year of operation, GTR and preoperative KPS did not significantly influence the occurrence of a new postoperative corticotropic deficiency ($p > 0.05$). The occurrence of complications significantly increased the risk for a new postoperative corticotropic deficiency ($r: 0.281, p < 0.01$) and the postoperative clinical outcome in terms of KPS (KPS, $r: -0.165, p: 0.018$).

Discussion

Compared to current literature, a new onset of anterior pituitary deficiency is described at approximately 2% up to 10% [19,4,9,31,8], depending on the surgical approach which is consistent with our presented results.

Long-term corticotropic deficiency requiring medical substitution with hydrocortisone occurred in 30.9% of all cases, in 10.4% the deficiency was new, 9% of the patients with preoperative corticotropic deficiencies had intact pituitary hormone secretion at follow-up of minimum 1 year.

Our results show a higher rate of postoperative improvement of preoperative manifest hormone deficiency, as current literature reports of a laboratory normalization of 3% after 6 months for the cortisol axis. We also identified a higher rate of new corticotropic deficiency compared to the stated 6% of new postoperative corticotropic deficiency in current literature [17]. Compared to other tumors of the sellar regions, these percentages seem very low (craniopharyngiomas: up to 53% of postoperative corticotropic deficiency after TSS [22], and rate of corticotropic deficiency after resection of Rathke's cleft cyst: 24% [21]). As these tumors were excluded from the analysis, no comparison between current literature and our results can be made concerning other sellar tumors than pituitary adenoma.

Cut-off values and timing of analysis

While detection of new corticotropic deficiencies is of main interest, to prevent Addison's crisis, we found different values for the sensitivity and specificity of laboratory cortisol testing direct postoperatively, 6-12 weeks after surgical treatment and 1 year after surgery. Of course, the closer the laboratory analysis coincides with the long-term follow-up clinical examination, the more sensitive and specific it becomes as some patients recover from postoperative hormone deficiencies and some patients tend to develop a secondary corticotropic deficiency. Our main interest is therefore to question the use of direct postoperative basal cortisol assessment if its use is very limited.

Limitations

Our study analyzed patients retrospectively, but complete long-term follow up data was available for a considerably large series of 211 patients. Unfortunately, the burden of disease caused by long-term hormone substitution has not been evaluated yet and was not included in our data examination. Symptoms of corticotropic deficiency, such as fatigue and impairment of daily living activities [11] are therefore not stated or described in our study. Therefore, we cannot assess the overall burden of disease caused by the transnasal surgical resection of pituitary adenoma. We unfortunately did not evaluate the subjective disability experienced and the prospective assessment of quality of life and impairment of daily living activities would give beneficial information on the overall treatment benefit or risks for patients treated surgically for pituitary adenoma [11].

Furthermore, patients were only included and analyzed, if complete endocrinological and clinical follow-up data was available. A bias is therefore included and needs to be discussed, potentially including more patients with complications and postoperative deficiencies in the analysis because of their increased need of postoperative supervision and follow-up appointments. Therefore, the evaluated 10% rate of new postoperative corticotropic deficiencies is most probably overrated in our patient cohort.

As we aimed to focus on corticotropic deficiency, we did not assess other pituitary deficiencies such as the often-frequented hypogonadism in male patients which presents a limitation of our study.

Prediction of long-term corticotropic deficiency

The exact cut-off value of cortisol serum levels to determine corticotrophic deficiency and its appropriate timing of testing (laboratory value measured in $\mu\text{g}/\text{dl}$ in morning serum) is still matter of debate [20,6,32]. Usual published cut-off values range between $4\mu\text{g}/\text{dl}$ [18] to $8\mu\text{g}/\text{dl}$ [6] to $14\mu\text{g}/\text{dl}$ [18]. In our study, we classified patients based on their actual clinical need of cortisone substitution regardless of their serum cortisol levels, which may over- or underestimate the real fraction of hormone deficient patients due to false interpretation symptoms such as fatigue. The measured and assessed cortisol cut-off value of $8.35\mu\text{g}/\text{dl}$ is congruent with and within the range of published data. Patients with basal serum cortisol levels above $>10\mu\text{g}/\text{dl}$ were declared as "hormone deficient" if they still presented with symptoms of hypocortisolism and had the clinical need for hydrocortisone supplementation with symptoms of hypocortisolism when the hydrocortisone administration was reduced (mostly symptoms of fatigue). False high basal cortisol levels due to either ingestion of hydrocortisone before blood testing (24 h off replacement hydrocortisone) or even factitious ingestion of hydrocortisone [1] were tried to be accounted for but cannot be excluded completely and may increase the uncertainty around a specific "cut-off" value for intact corticotrophic function. Values from patients stating they had their hydrocortisone medication or food/ coffee intake before the blood was taken were of course excluded from analysis.

In our department, hydrocortisone supplementation is usually continued for 6 to 12 weeks after transsphenoidal surgery until the following endocrine laboratory testing, regardless of the assessed postoperative cortisol serum values. Side effects of supplementary (unnecessary) hydrocortisone administration could be prevented if the post-operative basal cortisol level or timing was more reliable and as early as possible, and direct postoperative testing obsolete if the positive predictive value is inferior to the long-term testing. Unfortunately, we did not assess possible consequences of supplementary (over-substituted) hydrocortisone substitution in terms of possible side effects such as high blood pressure, diabetic complications or osteoporosis. In order to assess the complete impact of false hydrocortisone administration, a prospective analysis of patients suffering from pituitary adenoma would be necessary, with a close attention to signs of under- or over-supplementation. Neither did we assess economic differences in term of cost-effectiveness of early versus late assessment of serum cortisol values and correct hydrocortisone substitution.

In total 66.3% if the patients underwent hydrocortisone substitution (substitution dosage of 10mg administered in the morning and midday for 6 weeks) while having intact postoperative pituitary function using our defined cut-off value. The use of direct postoperative cortisol level evaluation has previously been questioned regarding its utility in clinical practice and implication for further hydrocortisone substitution [28,16,25,13]. With the risk of Addison's disease, some patient may be rather over-supplemented, with the risk of long-term effects of hypercortisolism [30]. Therefore, reliable cut-off values with a high positive predictive value and an optimal timing of analysis need to be provided. In our department, we shifted towards a more individual approach focusing on patients with very low postoperative cortisol levels and higher levels to present in our outpatient department earlier in order to adjust or stop the hydrocortisone substitution. We furthermore abandoned the strict cortisol cut-off value of $10\mu\text{g}/\text{dl}$ and focus more on the clinical and functional status of the patient after with-drawing the hydrocortisone substitution. Nevertheless, the higher mortality caused by hypocortisolism [10] compared

to risks caused by over-supplementation of hydrocortisone may shift the optimal early cut-off value for basal cortisol towards a higher sensibility at the cost of a lower specificity.

Conclusion

In 30.9% of all patients, long-term hydrocortisone substitution was necessary to support the adrenocorticotrophic axis in patients with corticotrophic deficiency. Prediction of hormone, especially corticotrophic deficiencies remain an important matter of debate in the neurooncological context, the duration of hydrocortisone substitution and timing of evaluation should therefore be questioned. In our study, evaluated cut-off values were congruent with published literature, and substitution in patients with intact postoperative pituitary function should be discussed further to reduce the risk of potential side effects. An improvement in reliability and prognostic quality of laboratory testing may reduce hydrocortisone oversupply without increasing the amount of undetected postoperative hypocortisolism.

Declarations

- **Funding**

No funding to declare.

- **Conflict of interest/ Competing interests**

All authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this publication.

- **Availability of data and materials**

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

- **Code availability**

Not applicable

- **Ethics approval**

The research conducted has been performed in accordance with the [Declaration of Helsinki](#), ethics approval was obtained and the positive vote was registered under the number 230/20-S.

- **Consent to participate - Consent for publication**

Informed consent for publication and surgical treatment was obtained.

- **Authors' contributions**

VB, NS, AW, VS made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; VB has been involved in drafting the manuscript, JG has been involved in revising it critically for important intellectual content; JG, SB and BM given final approval of the version to be published. VB and JG agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Mean Hormone level	Preoperative	Early Postoperative	After 6-12 weeks	1 year after surgery
Basal Cortisol (µg/dl)	11.7	12.6	11.9	11.2
(95% CI)	(10.7-12.6)	(11.5-13.8)	(10.7-13.1)	(10.2-11.2)
In patients with corticotrophic hormone deficiency				6.01
	3.99			(4.2-7.8)
In patients without corticotrophic hormone deficiency	(3.2-4.8)			13.7
				(12.7-14.6)
	15.1			
	(14.2-16.0)			

Table 1. Preoperative hormone levels classified by timing of the analysis and classified in patients with corticotrophic hormone deficiency and intact pituitary function (“without hormone deficiency), 5 days after surgery (“early postoperative”), 6 to 12 weeks after surgery and 1 year after surgery with 95% CI (confidence interval).

Cortisol morning serum values (ug/dl)	Positive if Greater Than or Equal To ^a	Sensitivity	Specificity	Youden Index
Postoperative value	2.8	0.949	0.32	0.269
	6.9*	0.864	0.56	0.424
	<i>10.15</i>	0.729	0.64	0.369
	20.65	0.195	0.94	0.135
6-12 weeks after surgery	6.85	0.949	0.66	0.609
	6.95*	0.941	0.68	0.621
	<i>10.05</i>	0.746	0.78	0.526
	20.3	0.085	0.94	0.025
1 year after surgery	7.05	0.949	0.72	0.669
	8.35*	0.898	0.82	0.718
	<i>10.05</i>	0.805	0.84	0.645
	20.45	0.076	0.94	0.016

Table 2: Morning serum cortisol levels assessed on the fifth day after surgery (postoperative value), 6-12 weeks after surgery and one year after surgery. The optimum cut-off value is marked*. The lower and higher cortisol value describes the 95% sensitivity and 95% specificity. The Youden index describes the maximum potential effectiveness of a certain cut-off value.

Figures

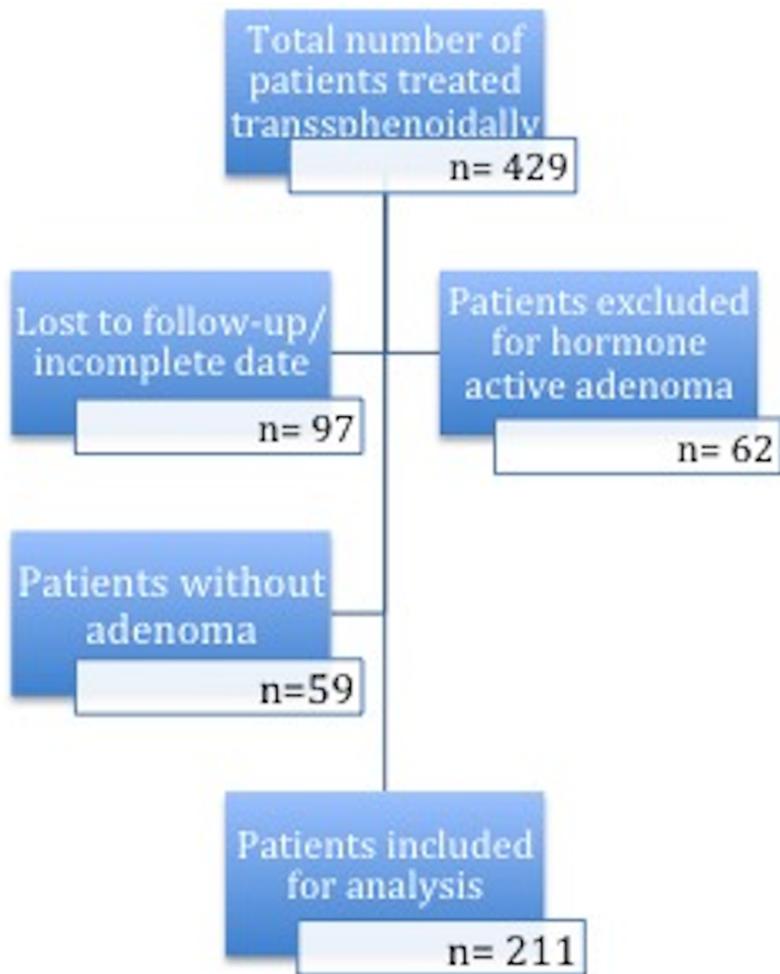


Figure 1

Flowchart describing the number of patients meeting the inclusion and exclusion criteria and showing the number of patients included for analysis (n= 211).

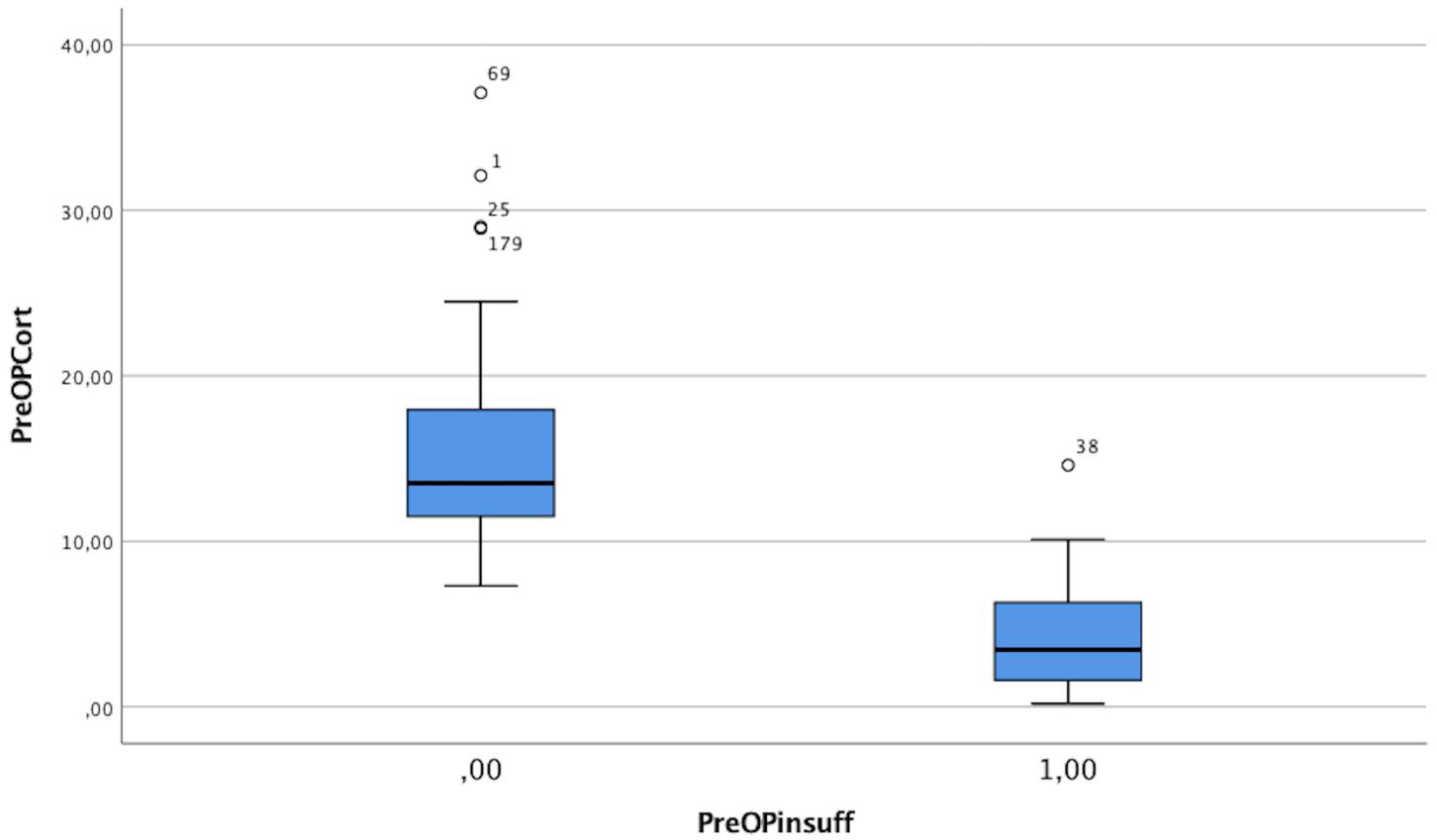


Figure 2

Distribution of basal cortisol levels depending on necessity of hydrocortisone substitution (0: no substitution, 1: hydrocortisone substitution) before surgery (in µg/dl).

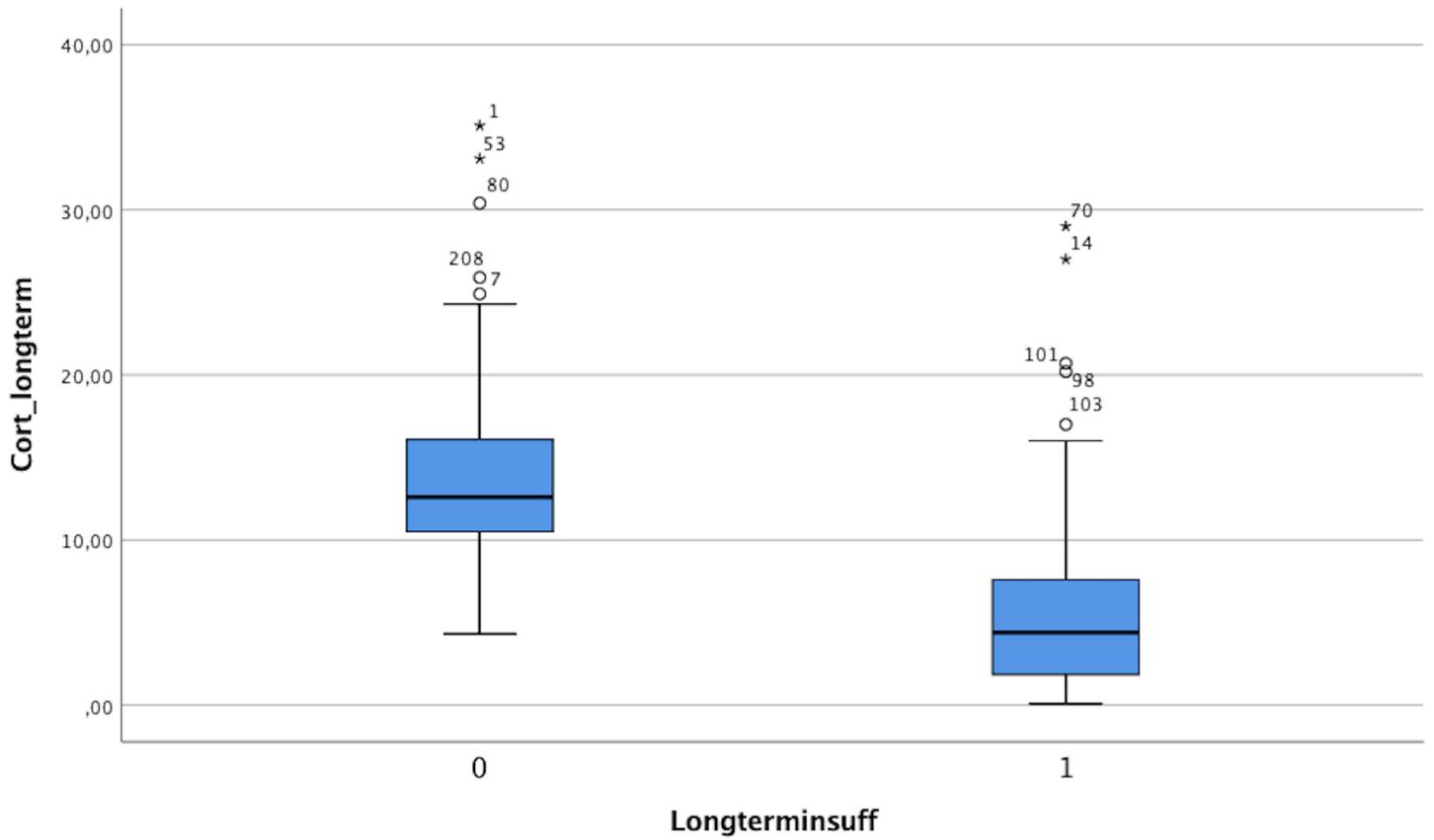


Figure 3

Distribution of basal cortisol levels depending on necessity of hydrocortisone substitution (0: no substitution, 1: hydrocortisone substitution) 1 year after surgery (in µg/dl).

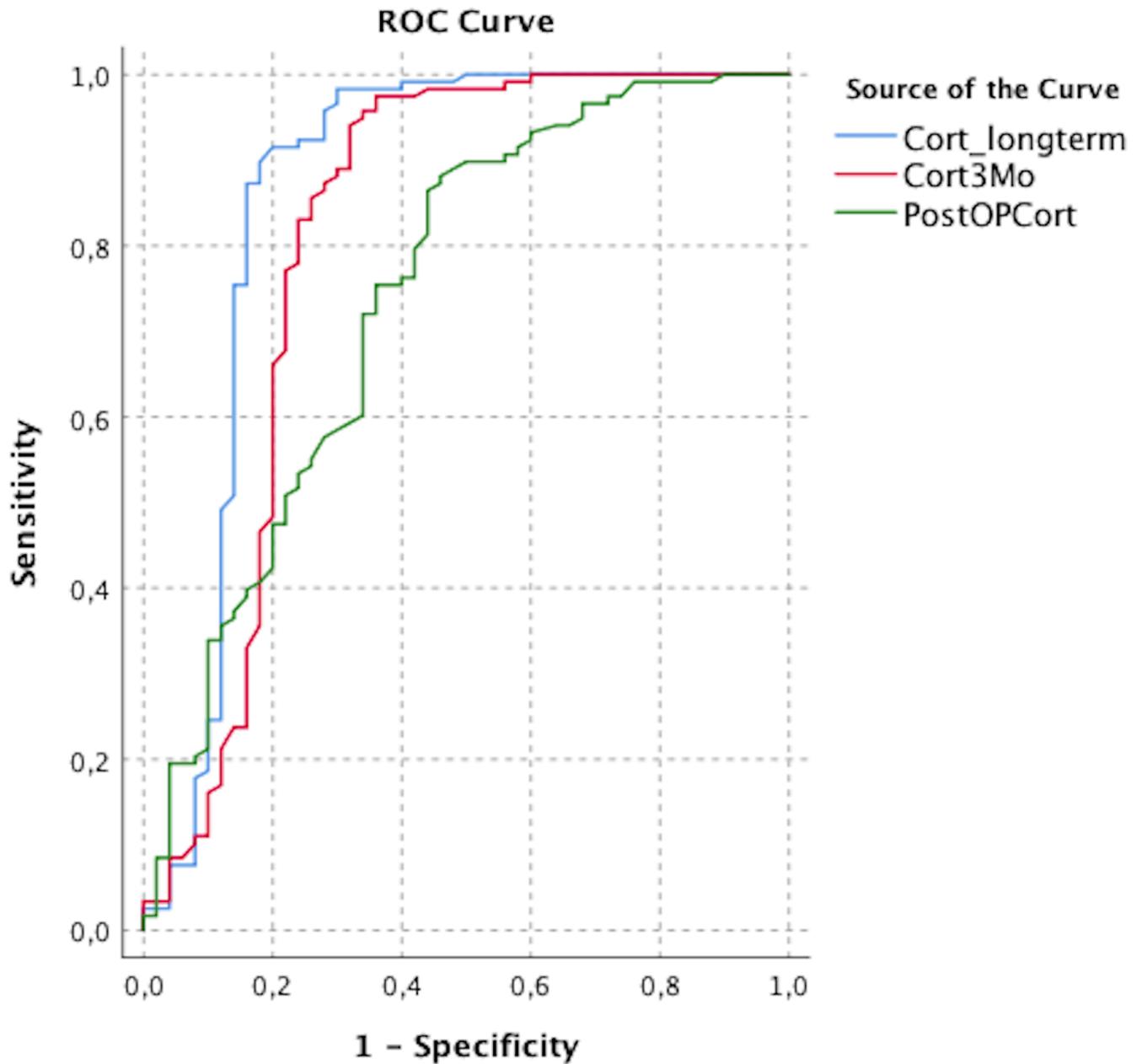


Figure 4

Receiver Operator Characteristic (ROC) curve showing the sensitivity and specificity of direct postoperative basal cortisol level, 3 months postoperatively and long-term, indicating a higher sensibility and specificity of the long-term cortisol compared to the direct postoperative cortisol level.