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Hormone outcomes following endoscopic endonasal resection of nonfunctional pituitary adenomas

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OBJECTIVE Resection of nonfunctional pituitary adenomas (NFPAs) can precipitate transient, or in some cases, permanent hormone deficits requiring replacement. Predicting the risk of permanent hormone dysfunction and the possibility of improvement postsurgery is crucial for patient counseling. This study analyzed a large cohort of patients with NFPA to assess predictors of postoperative hormone function and to help both surgeons and patients better predict outcomes.

METHODS The authors conducted a retrospective single-institution study on a series of patients treated for NFPAs at Weill Cornell Medicine between 2006 and 2023. Data including demographics, preoperative hormone status, laboratory values, pathological and radiographic tumor characteristics, and postoperative transient and permanent hormone replacement were collected. Multivariable logistic regression analysis was used to identify predictors of hormone deterioration and improvement.

RESULTS A cohort of 372 patients were included in this study, 56% of whom presented with preoperative hormone deficiency of at least one axis. A total of 79% of patients underwent gross-total or near-total resection. Postoperatively, 178 (48%) required permanent hormone replacement for at least one hormonal axis: thyroid (34%), cortisol (23%), gonadotropin (15%), and antidiuretic hormone (7%). In patients with no preoperative endocrinopathy, 30.8% needed new hormone replacement therapy. Apoplexy and tumor size were strong predictors. If the tumor was < 2 cm, 23.5% needed new hormone replacement, and if the tumor was > 3 cm, 54.5% needed new hormone replacement. On the other hand, 39.5% of patients with a preoperative hormone deficiency did not require any long-term replacement. If the tumor was < 2 cm, 53.3% improved, and if the tumor was > 3 cm, 32.7% improved. Factors significantly associated with permanent hormone replacement and improvement besides tumor size and the presence of preoperative hormone deficiencies included hemorrhage on MRI, age, and sex, but these associated factors differed for each axis.

CONCLUSIONS This study highlights the relatively high but balanced rates of hormone loss and improvement after surgical removal of nonhormone-producing adenomas. The size of the tumor, apoplexy, and the patient's preoperative hormone status are strong predictors of outcome and can be used to estimate hormone function after surgery.

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KEYWORDS hormone; pituitary adenoma; endonasal; endoscopic; pituitary surgery; transsphenoidal; outcome; tumor

Pituitary adenomas are benign tumors arising from the pituitary gland. Nonfunctional pituitary adenomas (NFPAs), which do not secrete active hormones, often remain undetected until they compress adjacent structures.[1] The goals of surgery are to achieve maximal safe resection of the tumor with anatomical preservation of the normal pituitary gland to preserve, hopefully improve, and/or prevent deterioration in hormone function.[2–7] Although improvement has been reported in anywhere from 20% to 40% of patients, resection can also precipitate transient, or in some cases, permanent hormone deficits requiring hormone replacement therapy.[8,9] The rate of hormone deficits following NFPA resection vary widely in the literature and depend on the hormonal axis.[10–15] For

ABBREVIATIONS ADH = antidiuretic hormone; EMR = electronic medical record; EOR = extent of resection; FSH = follicle-stimulating hormone; GH = growth hormone; GTR = gross-total resection; LH = luteinizing hormone; NFPA = nonfunctional pituitary adenoma; NTR = near-total resection; POD = postoperative day; PRL = prolactin; STR = subtotal resection.

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example, central diabetes insipidus can occur transiently in anywhere from 2% to 15%, and permanently in 0%–7% of cases.[16]

Understanding and predicting the risk of permanent hormone dysfunction and the possibility of improvement postsurgery is crucial for optimizing patient management and preoperative patient counseling. For example, prior studies have identified some preoperative predictors of postoperative hormone deficiency, such as size of tumor, male sex, hyperprolactinemia, and tumor consistency.[14,17,18] However, what is missing from the literature is a simple table that can be used as a quick reference to inform a patient of their chance of recovery or deterioration based on known preoperative factors. In this study, we analyze hormone outcomes in a large cohort of patients with NFPA by using multivariable logistic regression considering tumor characteristics, preoperative hormone status, and patient demographics to stratify patients according to their risk of developing permanent hormone deficiencies. In addition, we have created a series of tables that can be used to predict a patient's hormone outcome based on their preoperative hormone status and the size of their tumor.

Methods

This study was approved by the Weill Cornell Medicine institutional review board. Electronic medical records (EMRs) from 2006 to 2023 were queried to identify patients who underwent surgery for NFPA who had a minimum of 3 months of follow-up and no history of previous surgery or radiation therapy. Clinical records were reviewed to extract patient demographics, medications, laboratory test results (e.g., preoperative prolactin [PRL], sodium, and postoperative cortisol), and hospital course. Tumor pathology and hormone staining were extracted from pathology records, whereas tumor invasion, size, and appearance (e.g., cystic/hemorrhagic) were obtained from radiology reports and imaging review. Apoplexy was gathered from a combination of radiographic evidence of bleed, or a prior history of acute onset of headache and cystic change within the gland on MRI. Preoperative visual deficits were recorded if the patient was subjectively symptomatic or if there were abnormal results on a Humphrey visual field assessment.

Tumor size was defined as the largest diameter on preoperative MRI. Weight was stratified into the following categories: underweight (BMI < 18.5); normal (18.5 < BMI < 25); overweight (25 < BMI < 30); and obese (BMI > 30). Extent of resection (EOR) and recurrences were defined by the board-certified neuroradiologist's reports on the 3-month and last follow-up scans. EOR was stratified as gross-total resection (GTR, 100% removal); near-total resection (NTR, ≥ 98% removal); or subtotal resection (STR, < 98% removal). Perioperative and postoperative complications were extracted from the surgeon's operative and follow-up notes and the hospital and clinic EMRs, respectively.

Hormone Deficit/Outcome Definitions

Preoperative hormone deficits were defined using preoperative laboratory results and clinical assessment closest to the day of surgery in the EMR. Patients were deemed to have low gonadotropins if they were men with testosterone levels below the standard value of the test, women younger than 60 years with inconsistent menstrual cycles, or women older than 60 years with normal or low follicle-stimulating hormone/luteinizing hormone (FSH/LH). Hypocortisolism was defined as having an AM cortisol level < 5. Hypothyroidism and growth hormone (GH) deficiency were defined as a free thyroxine or insulin-like growth factor–I level below the lower limit of normal as defined by the standard value range for each test. Preoperative laboratory results were available for 83%–88% of included patients depending on the axis (Table 1). Patients who were missing preoperative data had their preoperative endocrine status imputed for our regression model. Partial hypopituitarism was reported for deficiency in any of the pituitary axes. Panhypopituitarism was defined as having hormone deficiencies in any 3 of the 4 hormones of interest. Sodium and AM cortisol values were also extracted from the EMR on postoperative day (POD) 6 (Na) and POD2 (cortisol) after resection. Preoperative hormone replacement (i.e., medications) were not tracked.

Postoperative hormone outcomes were defined based on requirement of long-term/permanent medical replacement with one of the following medications: hydrocortisone; dexamethasone; prednisone; prednisolone; methylprednisolone (permanent cortisol replacement); levothyroxine; liothyronine; natural thyroid tablets (permanent thyroid replacement); desmopressin (permanent antidiuretic hormone [ADH] replacement); testosterone/Axiron; clomiphene; estrogen; progesterone; medroxyprogesterone; and human chorionic gonadotropin (hCG; permanent gonadotropin replacement). Transient replacement was defined by medications prescribed immediately following surgery, at hospital discharge, whereas the threshold for permanent replacement was the patient's most recent outpatient follow-up appointment. Postoperative improvement in hormone deficiency was defined as having a preoperative deficit based on laboratory values, as described above, but not requiring permanent hormone replacement of that hormonal axis postoperatively (i.e., at last follow-up). Any postoperative improvement was defined as having any preoperative hormone deficiency with no long-term replacement of that axis postoperatively.

Statistical Analysis

The study focused on 5 primary outcomes based on permanent medication replacement, one for each hormone being studied (i.e., cortisol, thyroid, ADH, and gonadotropins), and a fifth focusing on a composite outcome (i.e., patients who required permanent medical therapy for any of the 4 hormones). For each outcome, multivariable logistic regression models with Firth correction were constructed. The variables considered in these models included demographics (e.g., sex, age, BMI); clinical characteristics (e.g., diabetes mellitus, clinical apoplexy); tumor staining; tumor characteristics (e.g., invasion, size); EOR (e.g., GTR, NTR); hormone status (i.e., whether or not the patient had any preexisting hormone deficiencies preoperatively based on endocrinological evaluation and laboratory results); and pre- and postoperative laboratory results (e.g.,

TABLE 1. Patient and tumor characteristics in 372 patients with NFPAs

Characteristic	Value
Clinical description	
Age in yrs	58.5 ± 14.4
Female	164 (44)
BMI in kg/m^2	29.0 ± 7.1
Diabetic	
Diabetic	57 (15)
Not diabetic	314 (84)
Unknown	1 (0.3)
Preop visual impairment	
Impaired	233 (63)
Not impaired	133 (36)
Unknown	6 (2)
Clinical apoplexy	
Apopleptic	40 (11)
Not apopleptic	330 (89)
Unknown	2 (0.5)
Median follow-up in mos (range)	17 (3–175)
Preop hormone deficiency	
Thyroid	
Deficient	88 (24)
Not deficient	222 (60)
Unknown	62 (17)
Cortisol	
Deficient	57 (15)
Not deficient	265 (71)
Unknown	50 (13)
Gonadotropins	
Deficient	144 (39)
Not deficient	180 (48)
Unknown	48 (13)
GH	
Deficient	40 (11)
Not deficient	289 (78)
Unknown	43 (12)
Panhypopituitarism	28 (8)
Preop laboratory values	
PRL	20.9 ± 21.4
Sodium	140.5 ± 3.4
Pathology staining	
ACTH-positive	30 (8)
PRL-positive	29 (8)
GH-positive	19 (5)
Radiographic characteristics	
Tumor size, mm	24.8 ± 10.0
Cystic	88 (24)
Hemorrhagic	35 (9)
Invasion	121 (33)
EOR	
GTR	280 (75)
NTR	15 (4)
STR	76 (20)
Unknown	1 (0.3)

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Unless otherwise indicated, values are expressed as the number (%) or the mean ± SD.

PRL, sodium). Using the same variables, we also modeled the odds of any postoperative hormonal improvement or improvement in specific hormonal axes (e.g., having preoperative hypocortisolism but postoperatively not requiring permanent cortisol replacement).

The analysis began by constructing univariate logistic regression models for each variable. Missing data were imputed using predictive mean matching for numeric variables, logistic regression imputation for binary variables, and polytomous imputation for categorical variables with more than two categories.[19,20] Variables that achieved significance at alpha = 0.15 in this preliminary analysis were then considered for the multivariable logistic regression. A backward stepwise selection approach was used to narrow these variables for analysis. For each of these selected factors, the adjusted odds ratio and its corresponding 95% confidence interval were computed.

Results

A total of 372 patients met inclusion criteria, having undergone surgery for clinically confirmed NFPA with no history of previous surgery or radiation. There were 208 men (55.9%), and patients had an average age of 58.5 ± 14.4 years and a BMI of 29.0 ± 7.1. Visual impairment was the presenting symptom in 233 patients (63%) (Table 1). Forty (11%) patients presented with apoplexy and 57 (15%) had diabetes mellitus. The average tumor size was 24.8 ± 10.0 mm, with 121 tumors (33%) demonstrating cavernous sinus invasion and 35 tumors (9%) demonstrating hemorrhage as noted by an independent radiologist's interpretation of the preoperative MRI. Eighty-eight patients (24%) were noted to have cystic changes within their adenomas (Table 1). The median follow-up postresection was 17 months.

Preoperative Hormone Status

For the entire series of 372 patients, 210 (56%) presented with some type of hormone deficiency. For tumors < 2 cm, 41% were deficient; for tumors 2–3 cm, 61% were deficient; and for tumors > 3 cm, 67% were deficient. Gonadotropin deficiency was the most common preoperative deficit, with 144 (39%) patients presenting with either decreased testosterone, inappropriate LH/FSH, or inconsistent menstrual cycles. This was followed in descending order by hypothyroidism (88 patients, 24%); hypocortisolism

TABLE 2. Hormone replacement by tumor size and preoperative deficiency

	Normal Postop	Any Postop Hormone Replacement	Postop Cortisol Replacement	Postop Thyroid Replacement	Postop Gonadotropin Replacement	Postop ADH Replacement
All patients, n = 372						
Normal preop, n = 78	54 (69.2%)	24 (30.8%)	14 (17.9%)	16 (20.5%)	4 (5.1%)	5 (6.4%)
Any preop hormone deficiency, n = 210	83 (39.5%)	127 (60.5%)	59 (28.1%)	93 (44.3%)	46 (21.9%)	16 (7.6%)
Preop hypocortisolism, n = 57	17 (29.8%)	40 (70.2%)	27 (47.4%)	35 (61.4%)	16 (28.1%)	4 (7.0%)
Preop hypothyroidism, n = 88	20 (22.7%)	68 (77.3%)	29 (33.0%)	59 (67.0%)	25 (28.4%)	8 (9.1%)
Preop hypogonadotropism, n = 144	58 (40.3%)	86 (59.7%)	46 (31.9%)	57 (39.6%)	37 (25.7%)	10 (6.9%)
Preop hyperprolactinemia, n = 140	72 (51.4%)	68 (48.6%)	25 (17.9%)	51 (36.4%)	19 (13.6%)	6 (4.3%)
Tumor size <2 cm, n = 110						
Normal preop, n = 34	26 (76.5%)	8 (23.5%)	5 (14.7%)	5 (14.7%)	0 (0.0%)	2 (5.9%)
Any preop hormone deficiency, n = 45	24 (53.3%)	21 (46.7%)	7 (15.6%)	17 (37.8%)	3 (6.7%)	0 (0.0%)
Preop hypocortisolism, n = 12	5 (41.7%)	7 (58.3%)	2 (16.7%)	6 (50.0%)	3 (25.0%)	0 (0.0%)
Preop hypothyroidism, n = 15	5 (33.3%)	10 (66.7%)	3 (20.0%)	8 (53.3%)	2 (13.3%)	0 (0.0%)
Preop hypogonadotropism, n = 30	16 (53.3%)	14 (46.7%)	6 (20.0%)	10 (33.3%)	3 (10.0%)	0 (0.0%)
Preop hyperprolactinemia, n = 29	17 (58.6%)	12 (41.4%)	2 (6.9%)	10 (34.5%)	1 (3.4%)	0 (0.0%)
Tumor size 2–3 cm, n = 165						
Normal preop, n = 30	22 (73.3%)	8 (26.7%)	3 (10.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)
Any preop hormone deficiency, n = 101	38 (37.6%)	63 (62.4%)	29 (28.7%)	41 (40.6%)	27 (26.7%)	6 (5.9%)
Preop hypocortisolism, n = 25	6 (24.0%)	19 (76.0%)	13 (52.0%)	17 (68.0%)	6 (24.0%)	1 (4.0%)
Preop hypothyroidism, n = 43	10 (23.3%)	33 (76.7%)	14 (32.6%)	28 (65.1%)	13 (30.2%)	3 (7.0%)
Preop hypogonadotropism, n = 73	28 (38.4%)	45 (61.6%)	24 (32.9%)	27 (37.0%)	22 (30.1%)	2 (2.7%)
Preop hyperprolactinemia, n = 69	35 (50.7%)	34 (49.3%)	13 (18.8%)	22 (31.9%)	12 (17.4%)	1 (1.4%)
Tumor size >3 cm, n = 82						
Normal preop, n = 11	5 (45.5%)	6 (54.5%)	5 (45.5%)	5 (45.5%)	2 (18.2%)	3 (27.3%)
Any preop hormone deficiency, n = 55	18 (32.7%)	37 (67.3%)	19 (34.5%)	31 (56.4%)	14 (25.5%)	9 (16.4%)
Preop hypocortisolism, n = 15	4 (26.7%)	11 (73.3%)	9 (60.0%)	10 (66.7%)	7 (46.7%)	3 (20.0%)
Preop hypothyroidism, n = 28	4 (14.3%)	24 (85.7%)	11 (39.3%)	22 (78.6%)	10 (35.7%)	5 (17.9%)
Preop hypogonadotropism, n = 36	12 (33.3%)	24 (66.7%)	14 (38.9%)	18 (50.0%)	10 (27.8%)	7 (19.4%)
Preop hyperprolactinemia, n = 37	18 (48.6%)	19 (51.4%)	8 (21.6%)	17 (45.9%)	5 (13.5%)	4 (10.8%)

A total of 15 patients did not have tumor size available preoperatively.

(57 patients, 15%); and GH deficiency (40 patients, 11%). PRL elevation, likely related to stalk effect, was present in 140 patients (38%), with an average preoperative PRL laboratory value of 20.9 ± 21.4.

EOR and Histology

EOR was GTR in 280 (75.3%), NTR in 15 (4.0%), STR in 76 (20.4%), and no data in 1 (0.3%). ACTH, GH, and PRL staining was present in 30 (8%), 19 (5%), and 29 (8%) tumors, respectively. However, they were not clinically functional (i.e., silent) despite positive staining (Table 1).

Postoperative Hormone Replacement

In the entire group, regardless of preoperative hormone status, transient replacement rates by each hormone were as follows: thyroid (144, 39%); cortisol (130, 35%); gonadotropins (59, 16%); and ADH (35, 9%). Postoperatively, 178 (48%) required permanent hormone replacement for at least one hormonal axis: thyroid (34%), cortisol (23%), gonadotropin (15%), and ADH (7%).

The rate of replacement by preoperative status is shown in Table 2 and Fig. 1. In patients with no preoperative endocrinopathy, 69.2% remained normal postoperatively, indicating that 30.8% needed new hormone replacement therapy: thyroid 20.5%, cortisol 17.9%. Tumor diameter was an important predictor. If the tumor was < 2 cm, 23.5% needed new hormone replacement. If the tumor was > 3 cm, 54.5% needed new replacement. If a patient had hypothyroidism preoperatively, the chance of requiring permanent thyroid replacement was 67% for all patients (53.3% for patients with tumors < 2 cm, and 78.6% for tumors > 3 cm). If a patient had a preoperative cortisol deficiency, the chance of requiring permanent cortisol replacement was 47.4% for all patients (16.7% for patients with tumors < 2 cm, and 60% for patients with tumors > 3 cm). These results can be interactively assessed and viewed by readers at https://yinglistats.shinyapps.io/hormone_replacement_lookup_table/.

Postoperative Hormone Improvement

Of the patients with any preoperative hormone deficiency (n = 210), 83 (39.5%) had normal postoperative hor-

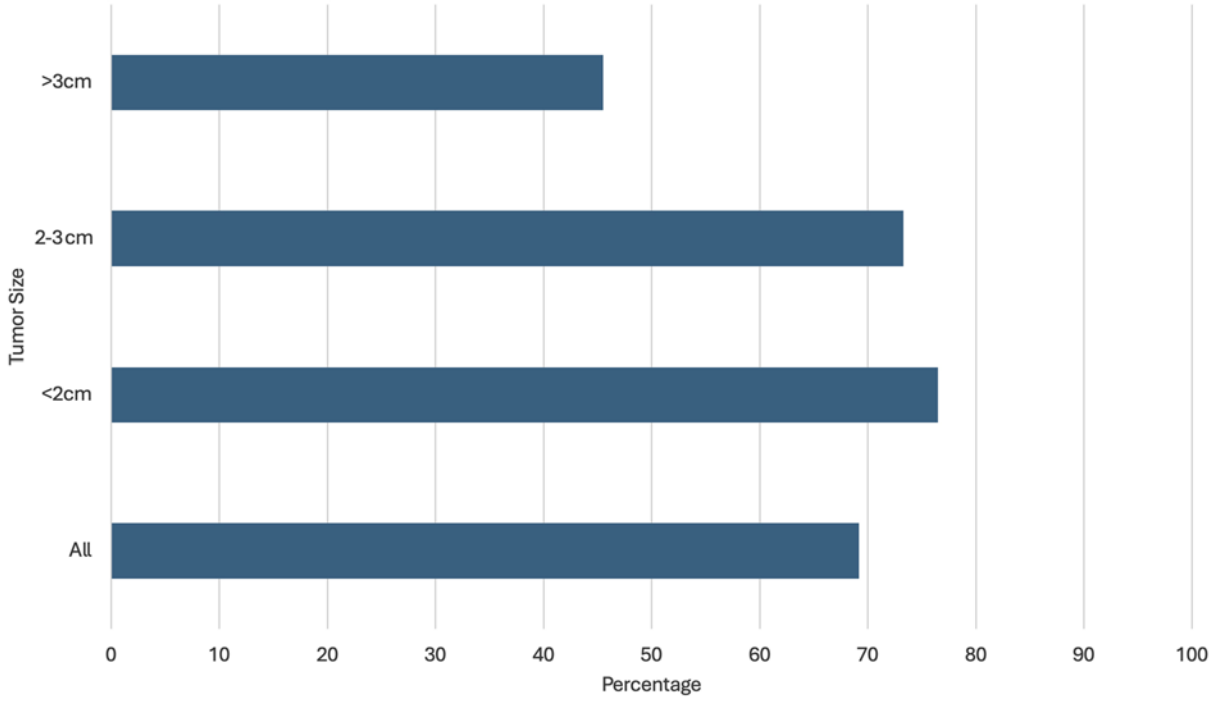

FIG. 1. Frequency of patients with no preoperative hormone deficits requiring no permanent hormone replacement, of any axis, based on tumor size. Figure is available in color online only.

mone function (not requiring permanent hormone replacement [Table 3]). Improvement rates also varied by tumor diameter. If the tumor was < 2 cm (n = 45), 53% improved. If the tumor was > 3 cm (n = 18), 33% improved. Improvement also varied by hormonal axis. For preoperative patients with hypothyroidism (n = 88), 29 (33%) were able to stop replacement. For preoperative patients with hypocortisolism (n = 57), 30 (53%) were able to avoid long-term replacement. Finally, for preoperative patients with hypogonadotropism (n = 144), 107 (74%) did not require permanent hormone replacement. Tumor diameter impacted hormone recovery for all axes (Table 3).

Multivariable Regression Analysis of Hormone Deterioration

A total of 178 (47.8%) patients had at least one type of permanent hormone dysfunction (i.e., requiring permanent cortisol, thyroid, ADH, or gonadotropin replacement postoperatively). Multivariable logistic regression identified 3 factors as statistically associated with requiring at least one permanent hormone replacement: hemorrhage on MRI (OR 2.17 [95% CI 1.00–4.74, p = 0.049]); preoperative hypothyroidism (OR 3.25 [95% CI 1.63–6.50, p = 0.001]); and number of preoperative hormone deficits (OR 1.45 [95% CI 1.02–2.07, p < 0.038]) (Table 4; Fig. 2).

No preoperative factor in this analysis correlated with all hormone outcomes. Increased tumor size was associated with increased risk of permanent cortisol and ADH replacement (OR 1.04 [95% CI 1.01–1.07, p = 0.002], and OR 1.09 [95% CI 1.05–1.13, p < 0.001], respectively). Tumor size was near significant in predicting permanent thyroid replacement as well (p = 0.06). Male sex was also associated with increased risk of requiring cortisol and gonadotropin replacement (OR 2.12 [95% CI 1.22–3.68, p = 0.007], and OR 18.10 [95% CI 5.05–64.96, p < 0.001], respectively).

In addition to tumor size and male sex, permanent cortisol replacement was also associated significantly with

TABLE 3. Improvement in hormone status by tumor size and preoperative deficiency

	Postop Hormone Improvement	All Patients, n = 372	Tumor Size <2 cm	Tumor Size 2–3 cm	Tumor Size >3 cm
Preop hormone deficiency					
Any preop hormone deficiency, n = 210	No permanent replacements	83 (39.5%)	24/45 (53.3%)	38/101 (37.6%)	18/55 (32.7%)
Preop hypocortisolism, n = 57	No permanent cortisol replacement	30 (52.6%)	10/12 (83.3%)	12/25 (48.0%)	6/15 (40.0%)
Preop hypothyroidism, n = 88	No permanent thyroid replacement	29 (33.0%)	7/15 (46.7%)	15/43 (34.9%)	6/28 (21.4%)
Preop hypogonadotropism, n = 144	No permanent gonadotropin replacement	107 (74.3%)	27/30 (90.0%)	51/73 (69.9%)	26/36 (72.2%)

A total of 15 patients did not have tumor size available preoperatively.

TABLE 4. Significant and near-significant predictors from logistic regression for permanent hormone replacement

	OR	95% CI	p Value
Any hormone replacement (n = 178, 48%)			
Preop hypothyroidism [yes (vs no)]	3.25	1.63–6.50	0.001
No. of preop hormones replaced	1.45	1.02–2.07	0.038
Hemorrhage on MRI [yes (vs no)]	2.17	1.00–4.74	0.049
Sex [male]	1.57	0.99–2.47	0.053
PRL staining [yes (vs no)]	0.40	0.15–1.05	0.057
Preop GH deficiency [yes (vs no)]	2.09	0.92–4.78	0.078
GH staining [yes (vs no)]	0.40	0.12–1.40	0.134
Thyroid replacement (n = 127, 34%)			
Preop hypothyroidism [yes (vs no)]	4.81	2.81–8.23	<0.001
Preop GH deficiency [yes (vs no)]	3.15	1.54–6.42	0.002
Preop hypocortisolism [yes (vs no)]	2.32	1.21–4.45	0.012
Age	1.02	1.00–1.04	0.038
Tumor size	1.02	1.00–1.05	0.061
PRL staining [yes (vs no)]	0.39	0.13–1.20	0.082
Hemorrhage on MRI [yes (vs no)]	1.85	0.85–4.01	0.127
Cortisol replacement (n = 85, 23%)			
Preop hypocortisolism [yes (vs no)]	2.97	1.59–5.57	0.001
Tumor size	1.04	1.01–1.07	0.002
Sex [male]	2.12	1.22–3.68	0.007
Clinical apoplexy [yes (vs no)]	2.55	1.21–5.37	0.017
POD2 cortisol	0.97	0.95–1.00	0.030
Preop hypogonadotropism [yes (vs no)]	1.48	0.88–2.51	0.146
GH staining [yes (vs no)]	0.36	0.07–1.96	0.186
Sex hormone replacement (n = 54, 15%)			
Sex [male]	18.10	5.05–64.96	<0.001
No. of preop hormones replaced	2.24	1.64–3.05	<0.001
POD2 cortisol (absolute value)	0.97	0.94–1.01	0.118
PRL staining [yes (vs no)]	0.34	0.06–2.06	0.206
ADH replacement (n = 25, 7%)			
Tumor size	1.09	1.05–1.13	<0.001
POD6 Na	1.14	1.02–1.28	0.016
Preop PRL level	0.96	0.93–1.00	0.021
Preop Na level	1.10	0.97–1.24	0.151

preoperative hypocortisolism (OR 2.97 [95% CI 1.59–5.57, p = 0.001]), clinical apoplexy (OR 2.55 [95% CI 1.21–5.37, p = 0.017]), and POD2 cortisol value (OR 0.97 [95% CI 0.95–1.00, p = 0.030]). Permanent thyroid replacement was significantly associated with preoperative hypothyroidism (OR 4.81 [95% CI 2.81–8.23, p < 0.001]), GH deficiency (OR 3.15 [95% CI 1.54–6.42, p = 0.002]) and preoperative hypocortisolism (OR 2.32 [95% CI 1.21–4.45, p = 0.012]), as well as with increasing patient age, with older patients at higher risk (OR 1.02 [95% CI 1.00–1.04, p = 0.038]). Permanent ADH replacement risk was increased with higher POD6 Na value (OR 1.14 [95% CI 1.02–1.28, p = 0.016]). Preoperative PRL elevation associated with lower rates of permanent ADH replacement (OR 0.96 [95% CI 0.93–1.00, p = 0.021]). Permanent gonadotropin replacement was significantly higher in patients with increasing numbers of preoperative hormone replacement (OR 2.24 [95% CI 1.64–3.05, p < 0.001]). A complete list of significant and near-significant predictors can be found in Table 4 and in Fig. 2. Interestingly, the EOR did not significantly associate with these outcomes.

Multivariable Regression Analysis of Hormone Improvement

Postoperative improvement in the cortisol, thyroid, and gonadotropin axes was associated with the number of preoperative hormone deficiencies (cortisol: OR 0.42 [95% CI 0.22–0.80, p = 0.005]; thyroid: OR 0.46 [95% CI 0.26–0.83, p = 0.005]; and gonadotropins: OR 0.49 [95% CI

FIG. 2. Heatmap of significant and near-significant predictors for hormone deterioration outcomes. *Light red blocks* represent predictors that reached significance at $p < 0.05$ for a given outcome, whereas *light blue blocks* represent near-significant predictors. Figure is available in color online only.

0.30–0.80, p = 0.003]), with a lower number of deficiencies associated with greater likelihood of improvement (Table 5; Fig. 3). For preoperative thyroid deficiency, tumor size and age also predicted improvement (OR 0.94 [95% CI 0.88–0.99, p = 0.021] and OR 0.97 [95% CI 0.94–1.00, p = 0.066], respectively), with larger tumors and increased age decreasing the odds of postoperative improvement. For gonadotropins, male sex was significantly associated with lower likelihood of improvement (OR 0.05 [95% CI 0.01–0.28, p < 0.001]).

Discussion

Although the goal of resection in pituitary macroadenomas is often tumor control or decompression of the optic pathways, the impact of resection on hormone outcome is a vital consideration in preoperative counseling. The present study provides a comprehensive analysis of hormone deficits and the chances of hormone recovery following endoscopic endonasal resection of NFPAs. Our findings corroborate previous research indicating a significant risk of permanent hormone deficiencies following NFPA resection, as demonstrated by the necessity for long-term hormone replacement therapy of at least one axis in 47% of patients,[21–24] with deficiencies in the thyroid and gonadal axes being the most common.[23,25] Approximately 30% of patients without preoperative hormone deficits were on at least one hormone replacement at last follow-up. This finding falls on the high end of the spectrum, which shows a wide range in the literature (approximately 1%–20%).[17,23–28] However, it is important to put this number into context, given that 56% of patients were deficient in at least one axis preoperatively, and new deficits were almost equally balanced by restoration of function in other patients. Furthermore, while the TRANSSPHER (Transsphenoidal Extent of Resection) study found lower rates of a new hormone deficit in endoscopic endonasal resections (9.7%), relative to our results, this comparison is confounded by the different definitions for hormone deficits.[29] The TRANSSPHER study used endocrine laboratory values, whereas we placed an emphasis on need for postoperative medication replacement. Furthermore, the earlier studies solely assess new deficit, whereas our study includes those with preexisting deficits in the permanent deficit group if they did not improve after surgery. It is unknown how microscopic resections may compare with our definition of hormone deficits.

The rate of postoperative improvement in this study (39%) is similar to that reported in the literature (approximately 40%–45%).[17,24] The variability throughout studies may be due to differing definitions for hormone deterioration/improvement and variable laboratory cutoffs. The outcome of interest in this study was defined as long-term

TABLE 5. Significant and near-significant predictors from logistic regression for postoperative improvement

	OR	95% CI	p Value
Any hormone improvement (n = 169, 80%)			
PRL staining [yes (vs no)]	3.20	0.58–17.76	0.129
Thyroid improvement (n = 29, 33%)			
No. of preop hormone deficits	0.46	0.26–0.83	0.005
Tumor size	0.94	0.88–0.99	0.021
Age	0.97	0.94–1.00	0.066
Cortisol improvement (n = 30, 53%)			
No. of preop hormone deficits	0.42	0.22–0.80	0.005
Preop Na level	1.12	0.97–1.29	0.121
Clinical apoplexy [yes (vs no)]	0.38	0.10–1.52	0.171
Sex hormone replacement (n = 107, 74%)			
Sex [male]	0.05	0.01–0.28	<0.001
No. of preop hormone deficits	0.49	0.30–0.80	0.003

medication requirement at last follow-up because this has a clinically meaningful impact on a patient's quality of life.

Overall, the strongest predictors of postoperative hormone deficiencies were the appearance of hemorrhage on preoperative MRI, the size of the tumor, and the total number of preoperative hormone deficiencies. Multiple other studies have also shown that hormone deficits at presentation predict hormone dysfunction postoperatively.[23,25] Hemorrhage serving as a strong predictor of the composite outcome suggests that intratumoral events may contrib-

FIG. 3. Heatmap of significant and near-significant predictors for hormone improvement outcomes. *Light red blocks* represent predictors that reached significance at $p < 0.05$ for a given outcome, whereas *light blue blocks* represent near-significant predictors. Figure is available in color online only.

ute to the extent of pituitary damage, thereby increasing the likelihood of permanent endocrinopathies, which is consistent with the literature.[30,31] Zhang et al. argue that hemorrhage is colinear with size, and thus size is the true predictor.[14,32,33] For our cohort, tumor size was shown to increase the risk of requiring replacement for cortisol and ADH, and was near-significant for thyroid hormone as well.

Interestingly, we found preoperative PRL elevation to be associated with lower rates of permanent ADH replacement. Mavromati et al.[17] found male sex and preoperative hyperprolactinemia to be predictive of hormone recovery. As has been previously suggested, elevated PRL levels preoperatively may indicate a functioning pituitary stalk, implying that the posterior neurohypophyseal system responsible for ADH secretion is less likely to be permanently damaged, ultimately reducing the risk of permanent ADH replacement. Unlike Mavromati et al., we found male sex to increase the risk of requiring cortisol replacement as well as gonadotropin replacement. This could in part be confounded by the significantly different rates of preoperative deficits when separated by sex at baseline in our cohort. Given that the average age of patients was 58 years, this may also simply be due to the fact that men this age are more likely to be on testosterone therapy for reasons unrelated to their NFPA. Ultimately, each axis generally had a unique set of predictors and there was no singular variable that predicted every hormone outcome. For example, increasing age was uniquely associated with thyroid replacement, whereas POD6 Na was uniquely associated with ADH replacement. Investigators have struggled to find universal predictors of worsening endocrine function postoperatively,[22] and each axis preservation clearly needs to be assessed independently.[23,25]

One of the primary goals of this study was to create an easy reference lookup table that a clinician could use to predict the outcome of any given patient. Tables 2 and 3 serve this function. If one plugs in the preoperative hormone status of any patient with a nonfunctioning adenoma and the size of the tumor, one can find the chances that the patient's postoperative hormones will deteriorate or improve based on the axis in question. Ultimately, data such as these, when accumulated across centers and providers, could be used to create a nomogram to help clinicians predict their patients' outcome with more certainty based on a variety of predictive factors.

This study was limited by its retrospective design, and its utilization of a single-center cohort. Single-center studies may limit generalizability given distinct patient populations and surgical approaches/techniques. Furthermore, thresholds for prescribing hormone replacement medications can depend on the treating endocrinologist and may not be universally applied. Patients were treated by a range of endocrinologists who may have applied different protocols, so these real-world outcomes must be interpreted in this context. This limitation is important given that our postoperative assessment was based on hormone replacement. Additionally, although our predictive model incorporates a variety of clinical parameters, the dynamic nature of endocrine function and the influence of intraoperative factors are difficult to control. Our model also uses imputation to assess issues with missingness for preoperative hormone status; although these methods are statistically validated in the literature, they are ultimately a well-reasoned estimate rather than objective. Our data also suggest that less aggressive STRs do not result in fewer postoperative hormone deficits. Although we assessed extent of resection as a variable, an alternative measure could have been residual tumor volume, which is less arbitrarily defined. However, ultimately the data suggest that unlike for functional pituitary adenomas, residual tumor is not likely to impact hormone outcomes for NFPAs. Last, variable follow-up times and use of hospital discharge as the definition for permanent and transient outcomes, respectively, may lead to over/underestimation of outcomes, but allowed for consistent definitions. Prospective, multicenter studies with larger sample sizes, integration of intraoperative details, inclusion of patients with recurrent or previously radiated/resected tumors, and improved data availability would provide further evidence for predicting permanent hormone outcomes following NFPA resection.

Conclusions

Our study represents one of the largest case series of NFPAs investigating endocrinological outcomes with a specific focus on need for long-term hormone medication replacement, providing vital information for preoperative counseling. In addition, we have created easy reference tables to predict outcome based on known preoperative factors. The factors identified in this study can help surgeons set reasonable patient expectations. With the growing focus on big data and machine learning, larger and more diverse patient populations can perhaps facilitate more precise endocrinological prognostication on an individualized patient basis.

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Disclosures

Dr. Schwartz reported being an investor in MIVI, Serenity Medical, Endostream Medical, BaseCamp Vascular, and Radical Catheter Technologies; he also reported membership on the Scientific Advisory Board of and stock options from Precision Neuroscience outside the submitted work.

Author Contributions

Conception and design: Bander, Gundlach, Tusa Lavieri. Acquisition of data: Schwartz, Bander, Pandey, Gundlach, Tusa Lavieri. Analysis and interpretation of data: Schwartz, Bander, Pandey, Li, Tusa Lavieri, Christos, Dobri. Drafting the article: Bander, Pandey, Gundlach. Critically revising the article: Schwartz, Bander, Pandey, Gundlach, Tusa Lavieri, Christos, Dobri. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Schwartz. Statistical analysis: Li, Christos. Administrative/technical/material support: Schwartz.

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