

## RESEARCH

# Prognostic usefulness of ACTH in the postoperative period of Cushing's disease

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## Abstract

**Objectives:** To analyze the usefulness of plasma ACTH in predicting CD remission after surgery and to evaluate the prognostic usefulness of ACTH measurement after the cortisol and ACTH nadir (48 h prior to discharge).

**Design:** A prospective study was made of 65 patients with CD operated upon between 2005 and 2016.

**Methods:** Postsurgery plasma ACTH and cortisol were measured every 6 h, in the absence of corticosteroid coverage. Hydrocortisone was started in the presence of adrenal insufficiency or cortisol <55.2 nmol/L. Plasma ACTH was again determined before discharge.

**Main outcome measure:** Usefulness of plasma ACTH in predicting CD remission.

**Results:** Remission at 3 months of CD was achieved in 56 of 65 cases, with late recurrence in 18 of 58 cases. Following resection, the ACTH nadir was significantly lower referred to late remission (2.8 vs 6.5 pmol/L;  $P = 0.031$ ) and higher for recurrence (2.1 vs 4.8 pmol/L;  $P < 0.001$ ), and identical results were obtained for the ACTH values before discharge. In the analysis of the ROC curves, nadir and before discharge ACTH values <1.9 pmol/L and <2.6 pmol/L were respectively indicative of early remission (AUC 0.827;  $P < 0.001$ ); <6.2 pmol/L of remission at 3 months (AUC 0.847;  $P = 0.001$ ) and >3.2 pmol/L of recurrence (AUC 0.810;  $P < 0.001$ ) in both ACTH values. A time to ACTH nadir <46 h was indicative of early remission (AUC 0.751;  $P = 0.001$ ), while a time >39 h was indicative of recurrence (AUC 0.773;  $P = 0.001$ ).

**Conclusions:** We propose an ACTH value <3.3 pmol/L as a good long-term prognostic marker in the postoperative period of CD. Reaching the ACTH nadir in less time is associated to a lesser recurrence rate.

## Key Words

- ▶ Cushing's disease
- ▶ ACTH
- ▶ cortisol
- ▶ transsphenoidal surgery
- ▶ remission
- ▶ recurrence

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## Introduction

Transsphenoidal surgery is the treatment of choice in Cushing's disease (CD). Following removal of the pituitary adenoma, the remission rate varies between 25 and 100% (mean 77.8%, median 78.7%), and the recurrence rate ranges from 0 to 65.6% (mean 13.2%, median 10.6%) (1, 2, 3, 4, 5, 6).

One of the most controversial aspects in the management of CD is the definition of remission criteria (7) and predictive factors.

Different CD remission predictors have been described in the literature, depending on the characteristics of the adenoma (aggressivity and spread, histology, size,

magnetic resonance imaging (MRI) identification of the adenoma, etc.), surgery and the experience of the neurosurgeon and biochemical criteria (8). In this respect, cortisol concentration in the immediate postoperative period has been the most widely used long-term prognostic indicator in most of the published series (1, 4, 6, 7, 8, 9, 10, 11, 12, 13).

The guidelines on the management of Cushing's syndrome published in 2015 (14) define CD remission as morning cortisol <5 µg/dL (<138 nmol/L) or urinary free cortisol (UFC) <10–20 µg/24 h (<28–56 nmol/24 h) in the 7 days after the operation. However, there is no consensus regarding the cortisol cut-off point after surgery (<5 µg/dL (137.9 nmol/L), <2 µg/dL (55.2 nmol/L), <1.8 µg/dL (49.7 nmol/L), <1.3 µg/dL (35.9 nmol/L) or even <1 µg/dL (27.6 nmol/L)) or the best time for determining cortisol: 24–48 h, 7–14 days or even months after surgery (6, 7, 8, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26).

Other functional tests have been described in the literature as predictors of recurrence, but they do not improve the results of postoperative basal cortisol, among which are: corticotropin-releasing hormone test (27), metyrapone test (28), desmopressin test (29, 30) and dexamethasone suppression test after desmopressin (31). For the interpretation of these last two tests, it is necessary to take into account if glucocorticoids are used in the perioperative period.

Few series have analyzed the usefulness of plasma ACTH after surgery as a prognostic indicator in CD, and the number of patients studied has moreover been very limited (6, 15, 25, 32, 33, 34, 35, 36, 37, 38, 39, 40). In patients with CD, it would seem reasonable to assume that the plasma ACTH values would decrease markedly in the first 12–24 h after complete removal of the pituitary adenoma, since the half-life of ACTH is about 10 min.

An ACTH cut-off point of <34 pg/mL (7.5 pmol/L) has been described for identifying patients in remission, with a sensitivity (S) of 80% and a specificity (Sp) of 97.5% (17), while other authors define a cut-off point of <10–20 pg/mL (2.2–4.4 pmol/L) as an indicator of adenoma resection (25, 38, 40). When interpreting the ACTH values, adequate sample processing must be considered, together with the fact that surgical stress (41) and/or manipulation could induce a transient peak.

## Study objectives

The primary objective of this study was to analyze the usefulness of plasma ACTH in predicting CD remission

in the immediate postoperative period (<72 h) and long-term remission.

The following secondary objectives were defined:

1. Establish early and late disease remission criteria according to plasma ACTH response in the immediate postoperative period and over the subsequent clinical course.
2. To evaluate the prognostic usefulness of ACTH measurement after the cortisol and ACTH nadir, and within the 48 h prior to discharge (expressed as the last ACTH measurement available in the postoperative period), and its possible correlation to CD remission and recurrence risk.

## Materials and methods

A prospective study was carried out involving 65 cases of CD (58 patients, with 7 reoperated cases) consecutively referred from 18 centers for surgical treatment between December 2005 and March 2016. The study protocol was authorized by the Ethics Committee of Hospital Universitario de la Ribera (Alzira, Spain), and written informed consent was obtained from all the patients.

Prior to the indication of surgery, bilateral inferior petrosal sinus sampling (BIPSS), with CRH stimulation and concomitant prolactin measurement, were performed on a regular basis in microadenomas measuring <6 mm in size or non-visible lesions at MRI, in order to confirm a pituitary origin.

- Perioperative management protocol:
  - The specific treatment for hypercortisolism (ketoconazole and/or cabergoline) was suspended before surgery (at least 1 week), avoiding the use of corticosteroids in the surgical phase. Imaging studies using neuronavigation protocols were made, together with a basal pituitary analysis upon patient admission for surgery.
  - A trans-naso-septal transsphenoidal approach was used, and all operations were performed by the same expert neurosurgeon. Although the guidelines do not establish a specific recommendation on the performance of hemi-hypophysectomy in those cases in which the adenoma is not identified during surgery, it seems a reasonable option to perform it based on BIPSS findings since prediction accuracy is high and remission rates are significant (42).
  - After surgery the patients were moved to intensive care, where plasma cortisol and ACTH

were determined every 6 h. ACTH sampling and assay were standardized to minimize errors in the measurements. Hydrocortisone was only administered when adrenal insufficiency was confirmed, with suggestive clinical manifestations (mainly arterial hypotension) and/or a cortisol nadir of  $<2\mu\text{g/dL}$  ( $55.2\text{nmol/L}$ ) in asymptomatic patients.

- The patients were moved to the hospital ward once this nadir was reached, or once they were found to be clinically stable without having reached the nadir in the first 72 h. The serial cortisol and ACTH measurements were continued in this latter case. Plasma ACTH was again determined before hospital discharge at 8:00 h, and in case of secondary adrenal insufficiency prior to the dose of hydrocortisone.
- Laboratory methods:
  - Cortisol measurement was made using a competitive electrochemoluminescence immunoassay (Elecsys E-170, ROCHE) from 2005 to 2011, and since 2012 using direct chemiluminescence technology (ADVIA Centaur®, SIEMENS). Results were interchangeable and showed good agreement (43). The plasma cortisol reference values at 7:00–9:00 h were  $4\text{--}24\mu\text{g/dL}$  ( $110.4\text{--}662.2\text{nmol/L}$ ), the minimum detection value being  $0.5\mu\text{g/dL}$  ( $13.8\text{nmol/L}$ ).
  - The ACTH values were obtained by electrochemoluminescence immunoassay (Elecsys E-170, ROCHE) from 2005 to 2011, and since 2012 using a sequential immunometric assay with two chemiluminescent binding sites in solid phase (IMMULITE 2000 ACTH®, SIEMENS). Both assays have been compared, showing excellent correlation ( $R=0.99$ ) (44). The reference values were respectively:  $1.00\text{--}2000\text{pg/mL}$  ( $0.220\text{--}440\text{pmol/L}$ ) and  $15\text{--}65\text{pg/mL}$  ( $3.3\text{--}143\text{pmol/L}$ ), the minimum detection values being  $1\text{pg/mL}$  ( $0.220\text{pmol/L}$ ) and  $5\text{pg/mL}$  ( $1.1\text{pmol/L}$ ), respectively.
  - Urinary free cortisol (UFC) was determined in 24-h urine by chemiluminescence (Architect i2000, ABBOTT). The reference values were  $20\text{--}90\mu\text{g/24h}$  ( $55.2\text{--}248.4\text{nmol/24h}$ ), and the values were also expressed as the number of times above the upper limit of normal (ULN).
- Remission and recurrence criteria:
  - The criteria for early CD remission after transsphenoidal surgery were a cortisol nadir of  $<2\mu\text{g/dL}$  ( $55.2\text{nmol/L}$ ), together with the need for

replacement therapy with corticosteroids due to the secondary adrenal insufficiency.

- Remission at 3 months was defined as normality of the hypothalamic–pituitary–adrenal axis 3 months after surgery (cortisol suppression following dexamethasone, absence of UFC elevation and normal nocturnal salivary cortisol levels) or the persistence of secondary adrenal insufficiency treated with corticosteroids.
- Recurrence was defined by confirmed abnormal laboratory test findings (at least two tests were considered to define recurrence being one of them urinary cortisol (and at least two samples)), clinical stigmata and medication dependence after a late remission period.
- Data collection and analysis: The data were coded and entered in an MS Excel 2016 spreadsheet (Microsoft Office 365) for subsequent analysis using the IBM SPSS version 23.0 statistical package. Descriptive, bivariate and multivariate analyses (artificial neural networks (ANNs)) were performed, with the definition of prognostic cut-off points for the main variables based on analysis of the area under the ROC curves (AUC). The results are reported as the mean ( $\pm$  standard deviation (s.d.)). Statistical significance was considered for  $P<0.05$  in two-tailed contrasts.

Variables found to be statistically significant in the bivariate analysis were selected as candidates for input into the final ANN model. Sensitivity analysis (importance analysis) was performed to determine the optimum variables for construction of the final ANN model. An exploratory three-layer multilayer perceptron (MLP) ANN model with a back propagation algorithm was constructed for sensitivity analysis. The data were randomly divided into a training sample (80%) and a test sample (20%). Sigmoid transfer functions were used in the hidden and output layers. Gradient descent was used to estimate the synaptic weights. The initial learning rate was 0.4, and the momentum was 0.9. According to the results of the univariate and sensitivity analyses, a final three-layer feed-forward ANN model with a back propagation algorithm was constructed for all patients. The ANN model was trained with a maximum of 500 iterations and 10 tours.

The analysis for this study was made on August 1, 2016 as cut-off date, after a mean follow-up of 64.18 (32.53) months.

## Results

The baseline characteristics of the 65 operated cases (corresponding to 58 patients) are shown in Table 1. In addition to the seven reoperations in our series due to CD persistence or recurrence, a first operation had been performed in four cases in another center.

The pituitary adenoma was identified by MRI in 59/65: 43 were microadenomas and 16 macroadenomas, with a mean size of 8.3 mm (s.d. 6.3). The adenoma could be located intraoperatively in four of the six cases lacking an MRI image (Table 1). Resection proved macroscopically complete in 56/65 cases. In two cases hemi-hypophysectomy guided by BIPSS was performed. Remaining tissue on the MRI scan after surgery was absent in 60/65 and non-resectable cavernous sinus tissue was present in 3/65.

There were no postoperative complications in 40 of the 65 cases. The most frequent problems were transient diabetes insipidus (14 cases), which proved irreversible in only one case.

Table 2 shows the mean plasma cortisol and ACTH nadir concentrations after surgery, the time taken to reach them and the plasma ACTH level prior to hospital discharge. A correlation was observed between the cortisol nadir and the ACTH nadir ( $R=0.656$ , Spearman test;  $P=0.001$ ).

The impact of transsphenoidal resection upon the clinical course of CD was as follows: persistence in 7/65 cases; early remission in 38/65 (40 cases reached cortisol nadir  $<2 \mu\text{g/dL}$  ( $55.2 \text{ nmol/L}$ )) and 53 cases were prescribed glucocorticoids at discharge, with a mean glucocorticoid

treatment time of 16.4 (19.7) (1–117) months; late remission in 56/65 cases, with a mean remission follow-up time of 45.5 (34.8) (1–72) months; and recurrence in 18 of the 58 cases, with a mean time to recurrence of 22.9 (21.6) (1–72) months. There were four deaths in the course of follow-up (three due to ischemic heart disease and one due to pneumonia).

Statistically significant differences were observed in the diagnostic categories established by MRI prior to surgery with regard to the cortisol and ACTH nadir values, time to cortisol and ACTH nadir and the value of the last ACTH measurement (Table 2).

With regard to the impact of transsphenoidal resection upon the clinical course of CD, Table 3 reports the outcomes according to the MRI-based diagnostic category.

No statistically significant differences were found between the mean ACTH nadir and the last ACTH measurement. In both cases, the mean values were significantly lower in microadenomas, as well as for short- and long-term remission. Conversely, the mean values were higher in macroadenomas and in patients with persistence and recurrence of CD after surgery (Tables 2 and 4).

ANN analysis was performed of late remission and recurrence in order to identify predictors of good long-term prognosis. The ACTH nadir, ACTH at discharge and cortisol nadir values were found to be postsurgical variables of greater relevance in predicting remission at 3 months (AUC 0.988) (Fig. 1). The independent variables of greatest weight in predicting recurrence were ACTH at discharge, time to ACTH nadir and reintervention (AUC 0.932) (Fig. 2).

The area under the receiver-operating characteristic curve (AUC) was used to assess the accuracy of the association between postoperative ACTH nadir levels and non-persistence, early remission, late remission and recurrence. The optimum ACTH nadir predictive of persistence was  $>28.05 \text{ pg/mL}$  ( $6.2 \text{ pmol/L}$ ), with a sensitivity (S) of 71.4%, a specificity (Sp) of 91.2% and an AUC of 0.847 (95% confidence interval (95% CI) 0.666–1.000;  $P=0.003$ ). The optimum ACTH nadir predictive of early remission was  $<8.75 \text{ pg/mL}$  ( $1.9 \text{ pmol/L}$ ) (S 59.5%, E 92.6%, AUC 0.828 (95% CI 0.730–0.926);  $P<0.001$ ). The optimum ACTH nadir value predictive of remission at 3 months was  $<28.05 \text{ pg/mL}$  ( $6.2 \text{ pmol/L}$ ) (S 92.7%, Sp 66.7%, AUC 0.846 (95% CI 0.696–0.997);  $P<0.001$ ) and for recurrence  $>14.7 \text{ pg/mL}$  ( $3.2 \text{ pmol/L}$ ) (S 77.8%, Sp 79.5%, AUC 0.811 (95% CI 0.687–0.934);  $P<0.001$ ). We obtained similar cut-off results for ACTH determination before discharge (Fig. 3).

**Table 1** Baseline characteristics.

Qualitative variables	No of patients ( $n = 65$ )
Gender	
Female	53
Previous surgery in another center	
No	61
Yes	4
MRI identification of the adenoma	
No	6
Microadenoma	43
Macroadenoma	16
Quantitative variables	Mean (s.d.)
Age (years)	44 (13)
Adenoma size on MRI scan (mm)	8.3 (6)
Presurgery UFC/ULN	3.5 (2.8)
Presurgery cortisol (nmol/L)	687.4 (226.2)
Presurgery ACTH (pmol/L)	16.3 (12.2)

MRI, magnetic resonance imaging; s.d., standard deviation; UFC, urinary free cortisol; ULN, upper limit of normal (reference).

**Table 2** Cortisol nadir mean values and times, ACTH nadir mean values and times and ACTH before hospital discharge (last ACTH).

	MRI identification of the adenoma			SS <sup>a</sup> (P)
	Microadenoma (n = 43)	Macroadenoma (n = 16)	No imaging data (n = 6)	
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	
Cortisol nadir (nmol/L)	81.1 <sup>b</sup> (117.0)	254.1 <sup>b</sup> (305.4)	186.2 (342.1)	0.016
Time to cortisol nadir (h)	46.6 <sup>c</sup> (28.2)	84.3 <sup>c</sup> (38.7)	56.0 (29.7)	0.001
ACTH nadir (pmol/L)	3.1 <sup>b</sup> (3.6)	9.6 <sup>b</sup> (13.4)	2.6 (2.0)	0.011
Time to ACTH nadir (h)	46.6 <sup>b</sup> (33.0)	77.7 <sup>b</sup> (38.9)	38.0 (23.1)	0.006
Last ACTH measurement (pmol/L)	3.1 <sup>b</sup> (3.5)	9.6 <sup>b</sup> (13.4)	2.6 (2.0)	0.010
Time of last ACTH measurement (h)	130 (52)	162 (54)	111 (37)	0.061

<sup>a</sup>SS, statistical significance (ANOVA); <sup>b</sup>Significant differences between macroadenomas and microadenomas (Scheffe test and Bonferroni test;  $P < 0.05$ ); <sup>c</sup>Significant differences between macroadenomas and microadenomas (Scheffe test and Bonferroni test;  $P < 0.01$ ).

The cut-off points of the ACTH nadir affording a specificity of 100% would be 66.5 pg/mL (14.6 pmol/L) for persistence, 6.9 pg/mL (1.5 pmol/L) for early remission, 6.9 pg/mL (1.5 pmol/L) for remission at 3 months and 36.1 pg/mL (7.9 pmol/L) for recurrence, though at the expense of poorer sensitivity values of 57.1, 48.6, 32.7 and 22.2%, respectively.

A time to ACTH nadir of under 46 h was indicative of early remission (S 75.7%, Sp 74.1%, AUC 0.751 (0.619–0.882);  $P = 0.001$ ), while a time over 39 h was indicative of recurrence (S 69.2%, Sp 83.3%, AUC 0.773 (0.629–0.917);  $P = 0.001$ ). In the case of persistence and remission at 3 months, the ROC curves referred to the time to ACTH nadir were not valid, since AUC < 0.600.

Further AUC analyses were performed to assess the prognostic value of the cortisol nadir and time to reach it. The cortisol nadir predictive of early remission was < 1.95 µg/dL (53.8 nmol/L) (S 100%, Sp 92.6%, AUC 0.976

(95% CI 0.938–1.000);  $P < 0.001$ ). The optimum cortisol nadir value predictive of remission at 3 months was < 2.78 µg/dL (76 nmol/L) (S 82.1%, Sp 88.9%, AUC 0.952 (95% CI 0.900–1.000);  $P < 0.001$ ) (Fig. 4) and for recurrence > 1.33 µg/dL (36.7 nmol/L) (S 65%, Sp 88.95%, AUC 0.809 (95% CI 0.691–0.920);  $P < 0.001$ ), respectively.

Lastly, a time to cortisol nadir above 46.5 h was indicative of recurrence (S 70%, Sp 83.3%, AUC 0.769 (95% CI 0.642–0.896);  $P < 0.001$ ).

### Discussion

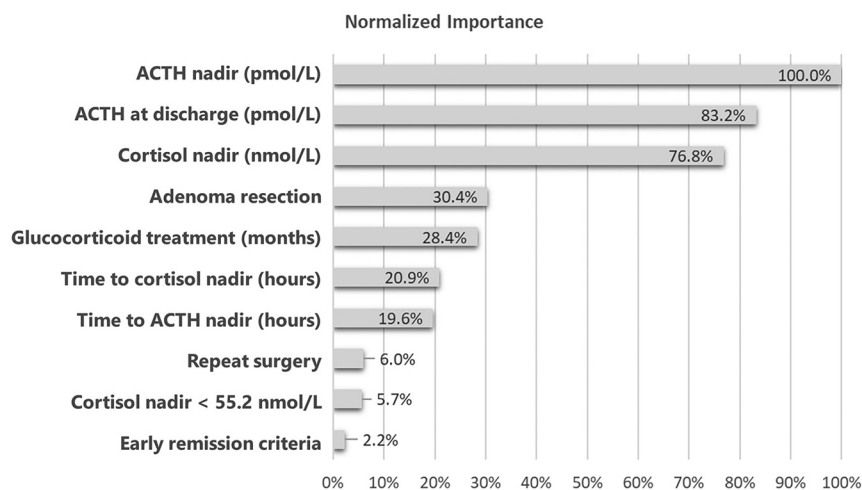
In our series, 86.2% (56/65) of the cases (93.02% (40/43) of the microadenomas, 75% (12/16) of the macroadenomas, and 66.7% (4/6) of the cases without MRI data) showed late remission after surgery. The mean remission rate reported in the literature is comparatively lower: 77.8% (82.2% microadenomas, 60.1% macroadenomas) (1, 6).

**Table 3** Impact of transsphenoidal resection according to adenoma identification by MRI.

	MRI identification of the adenoma				SS <sup>a</sup> (P)
	Microadenoma	Macroadenoma	No imaging data	Total sample	
	No of patients (n = 65) <sup>b</sup>				
Persistence after surgery					
No	40	13	5	58	0.383
Yes	3	3	1	7	
Early remission criteria					
No	14	10	3	27	0.105
Yes	29	6	3	38	
Remission at 3 months					
No	3	4	2	9	0.071
Yes	40	12	4	56	
Recurrence <sup>b</sup>					
No	29	7	4	40	0.386
Yes	11	6	1	18	
Repeat surgery					
No	37	14	6	57	0.622
Yes	6	2	0	8	

<sup>a</sup>SS: statistical significance (chi-squared test). <sup>b</sup>The cases of recurrence are analyzed with respect to the 58 cases in which CD did not persist after surgery.





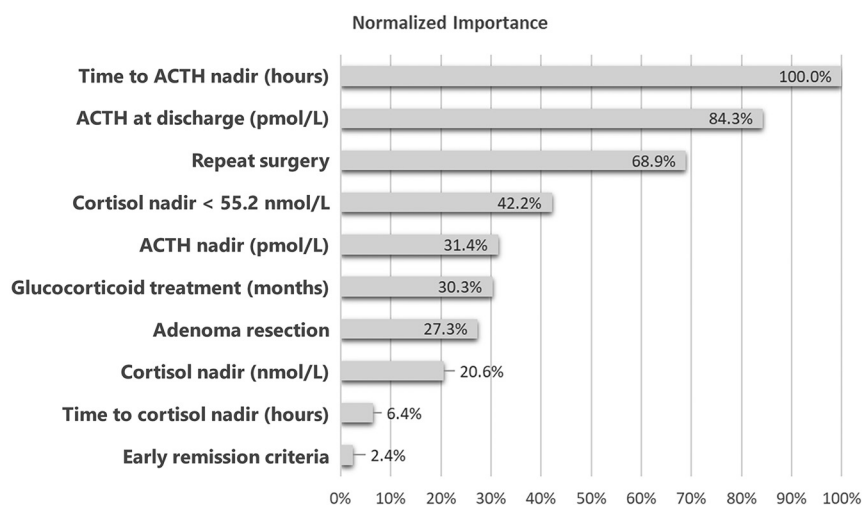
**Figure 1**  
Artificial neural network (ANN) analysis for predicting remission at 3 months of CD.

at discharge. This consolidates the results of the bivariate analysis and demonstrates the relevance of last ACTH measurement and the time taken to reach the lowest ACTH value in the immediate postoperative period.

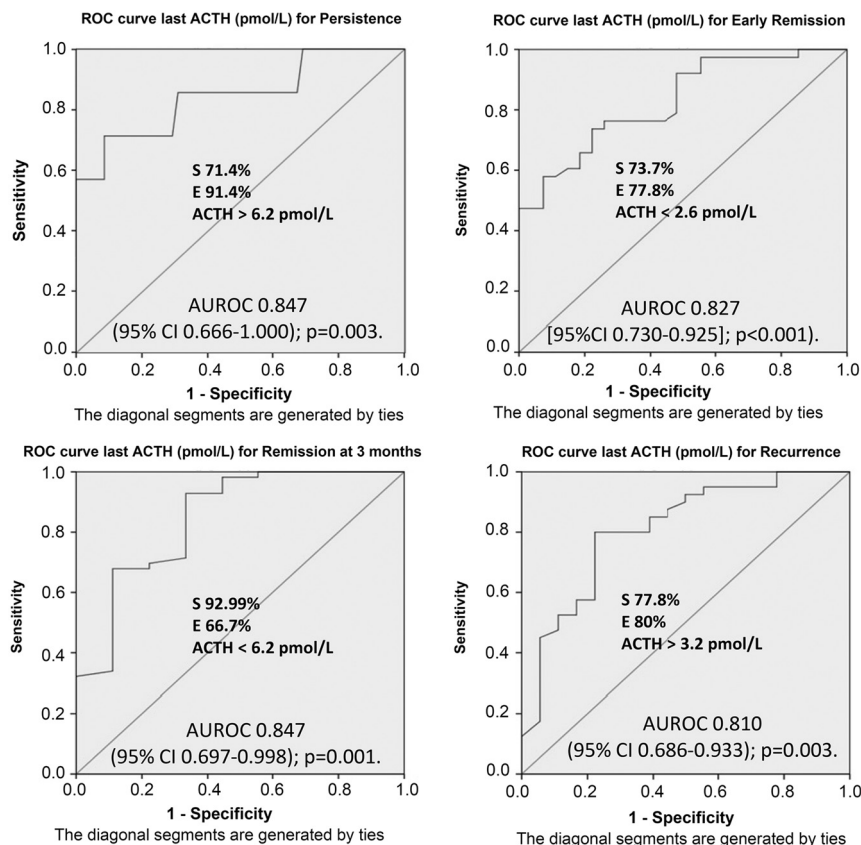
It is important to underscore that ANN is a multivariate statistical analysis that defines which independent variables have more weight in the prediction (>50% normalized importance). To our knowledge, this analysis has not been previously applied to CD predictive factors after surgery and demonstrates that ACTH values are even more important than cortisol values. The cortisol nadir is more important for predicting late remission than cortisol <2 µg/dL (52.2 nmol/L), which could indicate that lowest (nadir) values are better than a cut-off point.

In relation to the ACTH nadir and last measurement of ACTH before discharge, the cut-off point with the best sensitivity–specificity combination as established

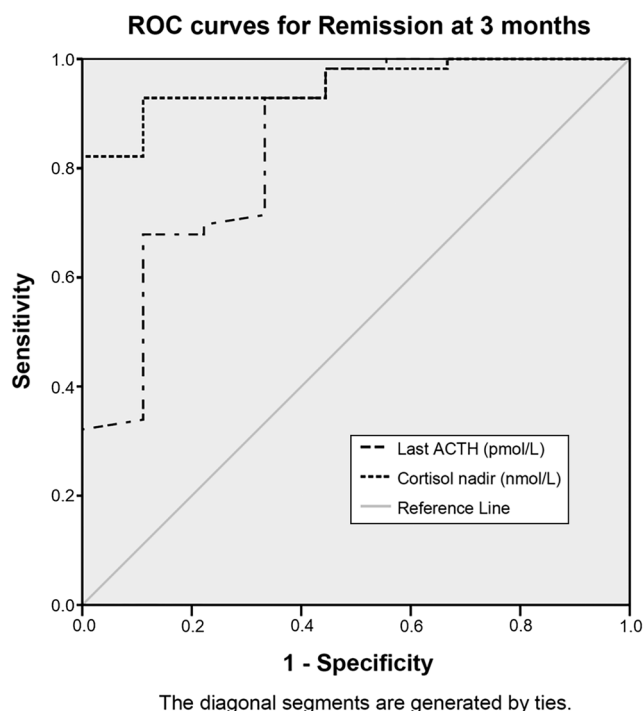
from the ROC curves was ≤15 pg/mL (3.3 pmol/L). This prognostic cut-off point of the ACTH nadir is similar to the values reported in the literature, ranging between 10 and 20 pg/mL (2.2–4.4 pmol/L) (35) and is clearly lower than the ACTH <34 pg/mL (7.5 pmol/L) level described by other authors (15). On the basis of our results, we propose an ACTH nadir and ACTH concentration before discharge of <15 pg/mL (3.3 pmol/L) as an indicator of good short- and long-term prognosis. The literature describes that reaching an undetectable ACTH nadir concentration, together with a cortisol level of <2 µg/dL (55.2 nmol/L), is associated to a greater probability of long-term remission (33). On reviewing the ACTH cut-off points after surgery in relation to the prognosis of CD, we found values of under 6.9 pg/mL (1.5 pmol/L) and over 36.1 pg/mL (7.9 pmol/L) to afford a specificity of 100% in identifying with remission and recurrence respectively, though the



**Figure 2**  
Artificial neural network (ANN) analysis for predicting recurrence of CD.



**Figure 3** Receiver-operating characteristic (ROC) curves corresponding to the determination of ACTH before hospital discharge. AUC, area under the receiver-operating characteristic curves; CI, confidence interval; S, sensitivity; Sp, specificity.



**Figure 4** Receiver-operating characteristic (ROC) curves corresponding to the determination of ACTH before hospital discharge and cortisol nadir value.

sensitivity is low. The differences between microadenomas and macroadenomas must be taken into account, since the latter are associated to higher postoperative cortisol and ACTH levels, and may take longer after surgery in reaching nadir concentrations. Indeed, the nadir may even be reached after patient discharge from hospital.

The timing of hypocortisolemia has been found to be critical in detecting late recurrences (8, 24, 26). However, the prognostic role of the time in reaching the ACTH nadir has been little described to date in the immediate postoperative period of CD. The dynamics of changes in plasma ACTH values after adenoma resection could also be of prognostic value, though the available data are limited and contradictory. An ACTH reduction of >40% after the first hour postsurgery (32) or an early and rapid decrease in ACTH values (15, 25, 33, 36, 37, 38) could discriminate those patients who will achieve late remission.

However, in other studies, plasma ACTH changes after surgery did not predict remission (34).

**Strengths and limitations**

This prospective study is the first to describe the prognostic usefulness of plasma ACTH measurement before hospital



discharge following transsphenoidal surgery – the prognostic utility being similar to that of the plasma ACTH nadir determined after the operation. ACTH measurement before discharge is less complex compared to serial determinations of ACTH. It can be performed routinely along with hormonal evaluation at discharge, without an apparent influence of replacement treatment. While the surgical technique and surgeon expertise can affect outcomes, all included patients underwent surgery at a single reference center. The short half-life of ACTH compared to cortisol, and the lack of effect of possible adrenal nodular hyperplasia on the delayed decline of cortisol should favor the usefulness of ACTH. However, it is complicated to generalize the use of postoperative ACTH. Each center should establish its own cut-off values, depending on the test used to measure ACTH, and taking into account the difficulties of standardizing extraction and analysis.

Although a mean follow-up time of 64.18 (32.53) months may seem sufficient, a longer duration of follow-up is required, since CD recurrence may occur as long as 10 years after surgery (2). Other limitations are the arbitrary definition of early remission based on a cortisol nadir of 2 µg/dL (55.2 nmol/L) and the possible influence of corticosteroid replacement therapy upon the ACTH levels (hydrocortisone was always used in our series, as it is more physiological and has a shorter half-life).

A more in-depth investigation into ACTH dynamics is needed in the immediate postoperative period in order to validate our results.

## Conclusions

In the immediate postoperative period of patients with CD, the ACTH concentration is of prognostic utility in relation to late disease remission. We propose an ACTH nadir of <15 pg/mL (3.3 pmol/L) as a good long-term prognostic indicator in CD following transsphenoidal surgery, referred to the prevention of recurrence. This same cut-off point is also applicable to the determination of ACTH before hospital discharge – the present study being the first to describe its relevance in predicting late disease remission and the absence of recurrence after transsphenoidal removal of the adenoma. Furthermore, reaching the ACTH nadir in less time is associated to a lesser recurrence rate.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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