Machine learning–based prediction of outcomes of the endoscopic endonasal approach in Cushing disease: is the future coming?

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OBJECTIVE Machine learning (ML) is an innovative method to analyze large and complex data sets. The aim of this study was to evaluate the use of ML to identify predictors of early postsurgical and long-term outcomes in patients treated for Cushing disease (CD).

METHODS All consecutive patients in our center who underwent surgery for CD through the endoscopic endonasal approach were retrospectively reviewed. Study endpoints were gross-tumor removal (GTR), postsurgical remission, and long-term control of disease. Several demographic, radiological, and histological factors were assessed as potential predictors. For ML-based modeling, data were randomly divided into 2 sets with an 80% to 20% ratio for bootstrapped training and testing, respectively. Several algorithms were tested and tuned for the area under the curve (AUC).

RESULTS The study included 151 patients. GTR was achieved in 137 patients (91%), and postsurgical hypersecretion remission was achieved in 133 patients (88%). At last follow-up, 116 patients (77%) were still in remission after surgery and in 21 patients (14%), CD was controlled with complementary treatment (overall, of 131 cases, 87% were under control at follow-up). At internal validation, the endpoints were predicted with AUCs of 0.81–1.00, accuracy of 81%–100%, and Brier scores of 0.035–0.151. Tumor size and invasiveness and histological confirmation of adrenocorticotrophic hormone (ACTH)–secreting cells were the main predictors for the 3 endpoints of interest.

CONCLUSIONS ML algorithms were used to train and internally validate robust models for all the endpoints, giving accurate outcome predictions in CD cases. This analytical method seems promising for potentially improving future patient care and counseling; however, careful clinical interpretation of the results remains necessary before any clinical adoption of ML. Moreover, further studies and increased sample sizes are definitely required before the widespread adoption of ML to the study of CD.

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KEYWORDS machine learning; outcome; predictors; Cushing disease; ACTH-secreting tumor; endoscopic endonasal surgery

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; AUC = area under the curve; CD = Cushing disease; CS = cavernous sinus; DI = diabetes insipidus; EEA = endoscopic endonasal approach; GBM = gradient boosting machine; GLM = generalized linear model; GTR = gross-tumor removal; IPSS = inferior petrosal sinus sampling; KNN = k-nearest neighbor; ML = machine learning; NPV = negative predictive value; PAS = periodic acid Schiff; PPV = positive predictive value; RF = random forest; ROC = receiver operating characteristic; SF-1 = steroidogenic factor-1; SVM = support vector machine.

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IN recent years, machine learning (ML) has been increasingly reported in the medical literature.^{22,40,44} ML is a branch of artificial intelligence science that allows the analysis of large amounts of variables and parameters: so-called “big data.”^{5,12,32} Progressive advancements in diagnostics and therapeutics have led to extraordinary increases in the number and complexity of collected data in medicine, in order to obtain the most comprehensive and multiaxial assessment of disease possible and to tailor its management on the basis of the specific features of each patient.^{5,12,32} The empowerment of modern computational machines has allowed the construction of complex models of artificial intelligence able to process enormous and heterogeneous data sets and to predict a disease or treatment outcome without being explicitly programmed. Indeed, after the creation of robust models using training data, ML can enable computers to perform automatic identification of predictive factors and learn complex risk factor interactions for the outcome(s) of interest in new patient cohorts.^{12,28,35,47–49}

Recent applications of ML to neurosurgery include segmentation of brain tumors and other critical targets (such as basal ganglia for deep brain stimulation), prediction of the location of an epileptic focus based on videoelectroencephalographic monitoring, stratification of clinical outcome after subarachnoid hemorrhage, and prediction of the results of surgery for intraxial brain tumor, dissection, or laminectomy.^{1,3,13–15,17,18,21,29–31,33,36,55–60,63,64} However, difficulties in the interpretation of ML results and the need for specifically trained research support staffs have prevented the wide adoption of ML in neurosurgery.^{9,51,52}

Pituitary surgery may represent an ideal field for the application of ML.^{24,37,57,60,61} Indeed, the management of pituitary tumors is very complex and requires a dedicated team made up of neurosurgeons, neuroendocrinologists, ENTs, neuroradiologists, and radiotherapists, flanked by ophthalmologists, oncologists, and neurologists.² Therefore, heterogeneous and sometimes controversial data, coming from biochemical assays, ophthalmological tests, neurological clinical and instrumental evaluations, and MRI and CT scan examinations, performed at diagnosis and follow-ups, have to be integrated and critically analyzed to assess patient outcomes.^{25,48,60,61,67}

Among the different pituitary afflictions, Cushing disease (CD) is one of the more challenging, with variable rates of remission and high risk of recurrence.^{6,27,48,57,66} Therefore, the outcomes of these patients are often the most difficult to predict preoperatively. The aim of this study was to evaluate the adoption of ML analysis for the identification of predictive models for the extent of tumor resection and postsurgical and long-term outcomes in a large and consistent cohort of patients with CD treated with an endoscopic endonasal approach (EEA).

Methods

The study included all consecutive patients with CD who underwent surgery via EEA during the period from May 1998 to December 2017 and had at least 12 months of follow-up at the Pituitary Unit, Center for the Diagnosis and Treatment of Hypothalamic-Pituitary Diseases,

IRCCS Institute of Neurological Sciences of Bologna, Italy.

CD diagnosis was based on clinical, biochemical, and radiological criteria, according to international guidelines.^{23,43,48} Patients who were treatment naïve and those who had already undergone treatment were included. Patients with Nelson’s syndrome or silent adrenocorticotrophic hormone (ACTH)–secreting adenomas were excluded. All surgeries were performed by a multidisciplinary team that included an expert pituitary neurosurgeon and a dedicated ENT surgeon, who followed a previously reported technique.^{19,20}

Preoperatively, patients underwent biochemical, endocrinological, neurological, and visual-field examinations and a 1.5-T MRI with gadolinium contrast medium. In cases with highly suspicious features or previous histological evidence of ACTH-secreting pituitary adenoma/cell hyperplasia but negative MRI findings, patients underwent 3-T MRI with gadolinium contrast medium and, if that was also negative, inferior petrosal sinus sampling (IPSS).⁴³

Based on MRI findings, lesions were divided into micro- (size < 1 cm), macro- (> 1 cm), or MRI-undetectable adenoma and then classified according to Hardy-Wilson score. If cavernous sinus (CS) invasion was suspected at preoperative MRI, it was classified according to Knosp grade and confirmed by direct surgical inspection.^{34,39,67}

Clinical, biochemical, radiological, and pathological data were retrospectively collected from patient records from the first hospital access to the last follow-up evaluation.

All slides were reviewed by an expert pituitary pathologist (S.A.). Histochemical stains included periodic acid Schiff (PAS) and Gordon-Sweet silver stain for reticulin, and immunohistochemical analysis was performed for pituitary hormones, pituitary transcription factor-1 (Pit-1), steroidogenic factor-1 (SF-1), estrogen receptor α (ER α), and cytokeratin CAM 5.2. Tumor invasion and proliferation were defined as > 2/10 mitoses per high-power field (HPF; 0.30 mm², $\times 400$ magnification), Ki-67 $\geq 3\%$, and p53 expression > 10 strongly positive nuclei/10 HPF in cells located within the areas with the highest nuclear labeling (hotspots).⁴⁵

Intra- and postoperative complications were reported to determine the surgical morbidity rate. Tumor resection was assessed as radical (no visible remnants) or nonradical (in case of visible tumor remnants) according to MRI performed 3 months after surgery (the first surgery in case of repeated procedures). Further MRI was performed every 6–12 months. Cortisol levels were checked at postoperative days 1 and 2 at 8 AM (a significant drop was considered for cortisol levels < 5 $\mu\text{g/dl}$).⁴² Cortisol levels were rechecked at the 1-, 3-, 6-, and 12-month follow-ups, and then annually, in cases with manifestations suggestive for hypocortisolism; levels < 2 $\mu\text{g/dl}$ defined CD remission. A low-dose ACTH test was performed in cases for which the cortisol levels were not clearly diagnostic.⁴² Postsurgical remission was defined for demonstrated hypersecretion normalization at 1 to 3–6 months after surgery (the first surgery in case of repeated procedures). In case of clinical manifestations or biochemical or MRI findings of

TABLE 1. Potential predictors and outcomes incorporated in ML analysis

	Patient & Neuroradiological Characteristics	Preop	Intraop	Postop
Potential predictors	Patient age & sex; diagnosis confirmed by IPSS; tumor size; Hardy, Wilson, & Knosp grades	Hypopituitarism, DI; previous operations; medical, radiation treatment	Bony tumor or cavernous invasiveness; CS invasion	Hypopituitarism, DI
Outcomes	—	—	GTR	Remission early postop or long-term (after op & other potential treatments)

alterations suggestive for disease recurrence, patients underwent appropriate screening for hypercortisolism (i.e., midnight salivary cortisol and/or dexamethasone [DEX] 1 mg).^{38,42} Other pituitary axes were tested according to timing and methods suggested by guidelines; replacement treatment was started in case of hormone insufficiency.⁴²

Patients also underwent surgical, ophthalmological, and neurological evaluations at 1, 3, 6, and 12 months of follow-up, and then annually. In addition, evaluations were also performed for manifestations suspicious for mass effects secondary to tumor remnant growth.^{38,42} Complementary treatments, such as postoperative medical and/or radiation therapies and bilateral surrenalectomy, were considered. Long-term biochemical outcome was defined based on disease control or persistence at last follow-up (cases for which bilateral adrenalectomy was performed were considered as not controlled).

The study was approved by an interhospital Ethical Committee of Bologna City (protocol CE17143, February 2018). Patients gave written informed consent authorizing the use of their clinical data anonymously.

ML Analysis

Potential predictors and outcomes are listed in Table 1. Continuous data are presented as mean $\pm$ SD and categorical data as numbers and percentages.

For ML-based modeling, data were randomly split into 2 sets in a 80%/20% ratio for training and testing, respectively. In the training set, the models were trained and continually validated using bootstrapping. Random forests (RFs), support vector machine (SVM), gradient boosting machine (GBM), Bayesian generalized linear models (GLMs), k-nearest neighbor (KNN), and decision trees based on the C5.0 algorithm, as well as artificial neural networks with a single hidden layer, were tested. After hyperparameter tuning, the model with the best performance during bootstrapping was selected based on the area under the curve (AUC) of the receiver operating characteristic (ROC), then evaluated on the test set for internal validation. Whenever relevant class imbalance was present, we applied synthetic minority oversampling (SMOTE) to the training set to ensure model robustness.⁵⁹ At internal validation, calibration (i.e., the degree to which predicted probabilities correspond to true, observed probabilities) was assessed using the Brier score (range 0–1, with values closer to 0 indicating greater calibration). AUC-based individual variable importance was obtained for each model. Final models were based on SVMs, RFs, and neural networks.

All analyses were carried out in R version 3.5.2 (The R Foundation for Statistical Computing). The statistical code is provided as Supplementary Content 1.

Results

Study Sample, Surgical Approach, and Histological Findings

In total, 151 patients (107 female, 70.8%) were included, for a total of 170 surgical procedures. The mean age at surgery was 41.1 ± 16.6 years, and 134 patients (88.7%) were treatment naïve, 17 (11.3%) had already undergone surgery, and 18 (11.9%) had already undergone medical therapy. Thirty patients (19.8%) presented with hypopituitarism, 9 (6%) with visual disturbances, and 6 (4%) with ophthalmoplegia (Table 2).

Adenomas were detected with preoperative MRI in 115 patients (76.2%); 80 were microadenomas (2 were ectopic, 1 located in the CS and the other in the pituitary stalk) and 35 were macroadenomas (Table 2). Intraoperative inspection demonstrated CS invasion in 7 cases (4.6%). A standard midline transsphenoidal approach was performed in 167 cases (98.2%), an ethmoido-pterigo-sphenoidal approach was performed in 2 cases of macroadenomas extending to the CS antero-inferior and lateral compartments, while the pituitary stalk microadenoma was removed through a supradiaphragmatic approach (Table 2).

An ACTH-secreting adenoma or diffuse corticotroph hyperplasia was detected in 82.4% of the cases at histological examination; in the other cases, the specimen was insufficient for diagnosis.

The morbidity rate was 3.4% and included epistaxis (n = 1), CSF leakage (n = 1), pneumonia (n = 3), myocardial infarction (n = 1), and pulmonary embolisms (n = 2). No surgical mortality was observed in the series.

Early Postsurgical and Long-Term Outcomes

Gross-tumor removal (GTR) was achieved in 137 cases (90.8%), while the postsurgical remission rate was 88.1% (133 patients; 95% in micro-, 82.6% in macro-, and 77.8% in MRI-undetectable adenomas). Disease persisted in 18 patients (11.9%; 6 macro-, 4 micro-, and 8 MRI-undetectable adenomas), with additional treatment of second surgery in 11 patients, radiation therapy in 8 patients, medical therapy in 5 patients, and bilateral adrenalectomy in 7 patients. Twenty-five patients (18.2%; 6 macro-, 11 micro-, and 8 MRI-undetectable adenomas) had disease recurrence after a mean of 5 years (range 1–16 years) and were treated with a second surgery (n = 12), radiation therapy (n

TABLE 2. Main demographic, clinical, and radiological features and previous treatments at the time of first surgery performed at our center

	Total (n = 151)	Males (n = 44)	Females (n = 107)
Age at diagnosis, yrs	39.7 ± 2.7 (14–79)	35.2 ± 5.5 (14–79)	41.8 ± 3.1 (14–75)
Age in yrs at 1st op at our center	41.1 ± 16.6 (14–76)	38.1 ± 18.0 (14–76)	42.3 ± 15.8 (14–76)
MRI features			
Macroadenoma (>1 cm)	35 (23.2)	13 (29.5)	22 (20.6)
Hardy grade ≥3	5 (0.33)	5 (11.4)	0 (0)
Wilson grade E	12 (7.9)	4 (9.0)	20 (18.7)
Knosp grade ≥3	6 (0.4)	4 (9.0)	2 (1.9)
Microadenoma (<1 cm)	80 (53.0)	20 (45.5)	60 (56.1)
Intrasellar	78 (51.7)	18 (41.0)	60 (56.1)
Ectopic	2 (1.3)	2 (4.5)	0 (0)
Undetectable adenoma	36 (23.8)	11 (25)	25 (23.3)
Previous medical therapy	18 (11.9)	6 (13.6)	12 (11.2)
Previous op	17 (11.3)	5 (11.4)	12 (11.2)
Hypopituitarism	30 (19.9)	12 (27.3)	18 (16.8)
Bitemporal hemianopia	6 (4)	2 (4.5)	4 (0.4)
Bitemporal quadrantanopia	1 (0.7)	1 (2.3)	0 (0)
Ophtalmoplegia	6 (4)	3 (6.8)	3 (2.8)

Values are presented as mean ± SD (range) or number of patients (%).

= 10), medical therapy (n = 4), or bilateral adrenalectomy (n = 6) (Tables 3 and 4).

Eighteen patients (11.9%) developed hypopituitarism and 27 (18%) central diabetes insipidus (DI; permanent in 6 and transient in 21). All 7 patients with preoperative bitemporal hemi-/quadrantanopia improved after surgery. Out of 6 patients with preoperative ophtalmoplegia, 4 (66.7%) recovered and 2 (33.3%) improved; no ophthalmological or neurological complications occurred (Tables 3 and 4).

At last follow-up (mean 92.3 ± 12.0 months), 116 patients (76.8%; 71.4% macro-, 83.8% micro-, and 66.7% MRI-undetectable adenomas) were in biochemical remission after single/repeated surgery and in 21 patients (13.9%) CD was controlled by complementary treatment, with CD considered under control at follow-up in 137 patients overall (Tables 3 and 4).

Cortisol levels dropped to under 5 µg/dl in 64 (71.9%) out of 89 patients (71.9%; 8 macro-, 42 micro-, and 14 MRI-undetectable adenomas), for whom an 8 AM sample on postsurgery day 1 or 2 was available. Sixty-one patients (95.3%) had long-term remission (56 after a single surgery and 5 after 2 surgeries), while 3 patients (5%) had

disease persistence. Eighteen (72%) of 25 patients without an early drop in cortisol levels had long-term disease remission, 12 (48%) after a single surgery, and 6 (24%) after 2 surgeries.

ML Analysis

A powerful and robust ML model was obtained for every outcome after extensive hyperparameter optimization (Tables 5 and 6).

The model predicting GTR was characterized by an AUC of 0.988; 96.8% accuracy, 96.4% specificity, and 100% sensitivity; 100% positive predictive value (PPV) and 75% negative predictive value (NPV); an F1 score of 0.982; and a Brier score of 0.035. Variables strongly associated with outcome were patient age, tumor visualization at preoperative MRI, tumor size < 10 mm, low Hardy-Wilson grade, histological confirmation of hyperplasia/adenoma, and postoperative hypopituitarism. As expected, Knosp grade, CS invasion, and persistent ACTH hypersecretion were negative prognostic factors (Tables 5 and 6).

The model predicting short-term postsurgical remission had an AUC of 1.00, with accuracy of specificity, sensitivity, PPV, and NPV of 100%, F1 score of 1.00, and Brier score of 0.097. The more relevant parameters associated with outcome were age and female sex, tumor visualization at preoperative MRI, size < 10 mm, low Hardy-Wilson grade, histological confirmation of ACTH adenoma, pre-/postoperative hypopituitarism, and presurgical medical treatment. Knosp grade, CS invasion, and persistent ACTH hypersecretion were negative prognostic factors (Tables 5 and 6).

The model predicting long-term disease cure after surgery or combined treatment presented an AUC of 0.783

TABLE 3. Surgical outcome

Disease Outcome	Total (n = 151)	Macroadenoma (n = 35)	Microadenoma (n = 80)	MRI Negative (n = 36)
Remission	133 (88.1)	29 (82.6)	76 (95)	28 (77.8)
Persistence	18 (11.9)	6 (17.4)	4 (5)	8 (22.2)

Values are presented as number of patients (%).

TABLE 4. Outcome at last follow-up

	Microadenoma (n = 80)	Macroadenoma (n = 35)	MRI-Undetectable Adenoma (n = 36)	Total
Remission after op only	67 (83.8)	25 (71.4)	24 (66.7)	116 (76.8)
Remission after op & complementary treatments	6 (7.5)	5 (14.3)	10 (27.8)	21 (13.9)
Uncontrolled disease	3 (3.8)	1 (2.9)	0 (0)	4 (2.6)
Death from pituitary carcinoma	0 (0)	1 (2.9)	0 (0)	1 (0.7)

Values are presented as number of patients (%).

and an accuracy of 80.7%. Sensitivity and specificity were 95.7% and 37.5% and PPV and NPV were 81.5% and 75.0%, respectively. The F1 score was 0.880 and the Brier score was 0.151. The more relevant prognostic factors of outcome were age and female sex, tumor visualization at preoperative MRI, size < 10 mm, low Hardy-Wilson grade, histological confirmation of ACTH adenoma, pre-/postoperative hypopituitarism, and presurgical medical treatment. Knosp grade, CS invasion, and persistent ACTH hypersecretion were negative prognostic factors (Tables 5 and 6).

Discussion

We have demonstrated in our large homogenous cohort of 151 patients who underwent CD surgery performed through EEA that ML is a reliable analytical method for predicting the extent of tumor removal and the chances of postsurgical remission and long-term control of disease. Indeed, at internal validation, all endpoints analyzed in this study were predicted with AUCs of 0.81–1.00, accuracy of 81%–100%, and Brier scores of 0.035–0.151.

CD is a very challenging condition, characterized by variable rates of remission and high risk of recurrence.^{9,10,24,42,43,46,50,53} Because of the lack of certain and reliable predictors, it is often difficult to predict each patient's short- and long-term outcomes.^{4,7,9–11,16,24,41–43,46,50,53,54,62} Indeed, in a large series of 230 consecutive CD patients who underwent surgery by EEA, Cebula et al. demonstrated that the presence of a microadenoma and histological confirmation of ACTH secretion were the only predictors of positive outcome.⁷ Conversely, Shin et al., analyzing 50 patients with CD treated through EEA, found no significant differences in the short-term remission rate among patients with micro-, macro-, or MRI-undetectable adenoma, while female sex and younger age were associated with a higher short-term (but not long-term) remission rate.⁵⁴ Finally, CS invasion tended to be associated with a more unfavorable outcome, although this finding did not reach statistical significance in their study.⁵⁴ As suggested by Shin et al., it could not be excluded that these difficulties in identifying certain prognostic factors may have been due to the small sample of CD series and the scant number of patients in each category, which could hamper statistical analysis.⁵⁴

Artificial intelligence methods of data analysis, such as ML, may overcome such limitations, revealing data associations otherwise not demonstrable.^{51,52,60} Indeed, differently from traditional statistics, these methods enable evaluation of the multitude of nonlinear interactions

among risk factors and therefore appear promising in the analysis of complex disorders such as CD.^{22,40,44} Supervised learning ML algorithms are based on the machine's ability to "learn" from labeled training data to produce predictive models, which are tested on previously unseen data.^{51,52,60} Differently from traditional programming models, which require a set of instructions provided manually by the operator to generate a desired output from input variables, in the ML algorithm the input and the desired outcome(s) are provided together.^{51,52,60} Then, the computer tries to define what rules combine the provided sets of data. Therefore, the final output of the algorithm is a predictive model whose accuracy is tested on a second set of data, not previously analyzed by the computer.^{51,52,60} Based on these theoretical premises, artificial intelligence may provide powerful and accurate prediction models to improve patient-tailored therapies and thus potentially improve patient care and counseling.⁵²

Specifically, ML has been applied to neurosurgery to improve preoperative diagnostic accuracy (i.e., for brain tumor segmentation, radiological segmentation, and detection of seizures at points of video electroencephalography and intraoperative tumor demarcation), and also for prediction (i.e., laterality of epileptogenic foci; patient survival in brain gliomas and after subarachnoid hemorrhage; and outcomes of epilepsy surgery, spine surgery, and deep brain stimulation for Parkinson disease).^{51,52,60} The application of ML to pituitary surgery is very preliminary but appears promising since some studies have demonstrated that ML accurately predicted the extent of tumor resection or postsurgical recurrence in EEA, as well as the risk of complications, particularly of postoperative CSF leak.^{24,37,57,60,61}

Our study confirmed the results of Shin et al. on the importance of sex and age for short-term biochemical remission, but it also demonstrated that these parameters, together with others such as tumor detection at MRI, size < 10 mm, Hardy-Wilson grade and histological confirmation of ACTH secretion, pre-/postoperative hypopituitarism, and presurgical medical treatment, also have predictive roles for long-term remission.⁵⁴ Moreover, our study demonstrated that tumor detection at MRI and size < 10 mm, as well as grade 1A Hardy-Wilson score and histological confirmation of ACTH-secreting cells, were associated with a higher chance of GTR. Jagannathan et al. suggested that the lack of postoperative disease control could be due to small tumor islets lying in the pseudocapsule, able to sustain hormone hypersecretion although undetectable at MRI.²⁶ According to our results, postsurgical

TABLE 5. Weight of each variable in the determination of GTR and early postsurgical and long-term disease remission according to 4 ML models applied to statistical analysis

Variable	GTR	Biochemical Remission Postop	Hypersecretion Control After Op & Treatments
Preop			
Female sex	2.4	13.9	14.3
Age in yrs	100.0	100.0	81.5
Tumor size			
Not visible	—	—	—
Microadenoma	5.9	81.2	20.9
Macroadenoma	3.3	9.1	7.8
IPSS	2.3	5.9	16.3
Hardy grade			
0	—	—	—
1	4.4	76.9	25.8
2	2.5	3.9	3.5
3	0.6	1.7	0.6
Wilson grade			
0	—	—	—
1	6.8	68.4	15.7
2	2.7	9.8	4.8
3	1.4	0.0	0.0
4	—	—	—
5	—	—	—
6	1.4	4.0	0.8
Knosp grade			
0	—	—	—
1	1.4	5.7	1.7
2	1.35	0.0	0.0
3	1.2	0.0	0.0
4	0.4	1.2	0.0
Intraop			
Invasion			
None	—	—	—
CS	1.9	0.1	1.1
Bone	1.3	0.0	0.0
CS & bone	1.6	0.0	0.0
ICSI			
None	—	—	—
CS compression	2.2	0.8	0.0
Focal	—	—	—
Diffuse	4.1	16.2	0.9
Lat compartment	0.7	0.9	0.0
Pituitary function			
None	—	—	—
Partial anterior hypopituitarism	1.4	12.7	13.2
Complete anterior hypopituitarism	0.0	0.0	0.0
Panhypopituitarism w/ DI	—	—	—
GH deficit	1.7	13.4	3.2
Gonadotroph deficit	4.5	5.1	2.8
Thyrotroph deficit	3.8	4.4	3.8
DI	2.6	0.0	0.0

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TABLE 5. Weight of each variable in the determination of GTR and early postsurgical and long-term disease remission according to 4 ML models applied to statistical analysis

Variable	GTR	Biochemical Remission Postop	Hypersecretion Control After Op & Treatments
Intraop (<i>continued</i>)			
Prior op	1.9	3.7	5.8
Prior medical treatment	3.9	16.8	15.6
Postop			
Histology			
No tumor	—	—	—
Corticotroph hyperplasia	10.5	0.0	0.0
ACTH adenoma	6.3	28.5	10.6
Persistent ACTH hypersecretion	33.2	25.2	100
GH deficit	1.8	12.1	0.2
Gonadotroph deficit	5.1	11.7	8.2
Thyrotroph deficit	2.0	5.9	18.7
Transient DI	1.6	33.9	2.6
Persistent DI	3.6	12.3	0.2

ICSI = intraoperative CS invasion.

Values were AUC derived and scaled to a 0–100 range.

hypopituitarism also appeared to be associated with a better chance of disease cure/control, but not with GTR. This finding may be explained by the fact that achieving radical resection of the tumor by also removing the pseudocapsule increases the chance of cure but also of pituitary damage, with consequent hypopituitarism. Higher Knosp grade exhibited a relatively low impact on CD remission, while the intraoperative demonstration of invasiveness was more strongly associated with negative short- and long-term outcomes, as suggested by Vallette-Kasic et al.⁶⁵

However, we consider all predictive models given by ML to require clinical interpretation before any use to avoid overemphasizing simple mathematical correlations with no endocrinological or surgical significance. Therefore, this study must be considered a preliminary experience, which should be confirmed by further studies. Its main strengths are the consistency of the study sample, the large number of available patient and tumor information, and the long-term follow-up. On the other hand, the retrospective design and the relatively small sample size, despite being among the largest available in the literature, together with the lack of 8 AM cortisol at postoperative days 1 and 2 in the majority of the patients, represent study limitations. The precision of the model predicting the long-term control of disease has been hampered by the heterogeneity in the postoperative complementary treatments, such as second surgeries, medical and radiation therapies, and the lack of control cases requiring bilateral adrenalectomy; however, all of these cases have been included to test ML outcome prediction in a real clinical scenario.

Conclusions

The complexity of CD in terms of clinical, radiological, and histological presentation, as well as associated diagnostic and therapeutic issues, makes this disease an

ideal candidate for ML analysis. Based on this preliminary evaluation, ML appears promising in predicting GTR as well as early postsurgical and long-term outcomes, thus improving patient-tailored care and counseling. On the

TABLE 6. Performance metrics of ML-based prediction models used on the training set and on the new data set (internal validation)

Performance Metric	Endpoint		
	GTR	Early Postop Remission	Long-Term Remission
Algorithm			
	KNN	SVM	GBM
Training (bootstrapping)			
AUC	0.993	0.681	0.719
Accuracy	96.3%	86.1%	74.3%
Sensitivity	97.0%	89.1%	82.4%
Specificity	88.9%	14.3%	35.4%
PPV (precision)	99.0%	96.1%	82.4%
NPV	72.7%	5.3%	40.5%
F1 score	0.980	0.925	0.838
Testing (internal validation)			
AUC	0.988	1.00	0.783
Accuracy	96.8%	100%	80.7%
Sensitivity	96.4%	100%	95.7%
Specificity	100%	100%	37.5%
PPV (precision)	100%	100%	81.5%
NPV	75.0%	100%	75.0%
F1 score	0.982	1.00	0.880
Brier score	0.035	0.097	0.151

other hand, for the same reasons, larger patient series and validations of predictive models in routine clinical settings are required to confirm the effectiveness of ML application in pituitary disorders.

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Disclosures

The authors report no conflict of interest concerning the materi-

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Conception and design: Zoli. Acquisition of data: Zoli, Friso, Rustici. Analysis and interpretation of data: Zoli, Staartjes, Friso, Rustici. Drafting the article: Zoli, Staartjes, Friso, Rustici, Sollini. Critically revising the article: Zoli, Staartjes, Guaraldi, Asiola, Sollini, Serra. Reviewed submitted version of manuscript: Zoli, Guaraldi, Asiola, Pasquini, Regli, Serra, Mazzatenta. Approved the final version of the manuscript on behalf of all authors: Zoli. Study supervision: Staartjes, Pasquini, Regli, Serra, Mazzatenta.

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