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Original research

The CuPeR model: A dynamic online tool for predicting Cushing's disease persistence and recurrence after pituitary surgery☆

Guive Sharifi [illegible], Elham Paraandavaji [illegible], Nader Akbari Dilmaghani [illegible], Tohid Emami Meybodi [illegible], Ibrahim Mohammadzadeh [illegible], Neginalsadat Sadeghi [illegible], Amirali Vaghari [illegible], Behnaz Niroomand [illegible], Seyed Mohammad Tavangar [illegible], Mohammad reza Mohajeri Tehrani [illegible], Zahra Davoodi [illegible], Marjan Mirsalehi [illegible], Seyed Ali Mousavinejad [illegible],**, Farzad Taghizadeh-Hesary [illegible],*

[a] Department of Neurosurgery, Loghman Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Skull Base Research Center, Loghman Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Clinical Research Development Center, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran
[d] Department of Otolaryngology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Neurosurgery Department, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[f] Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[g] Department of Pathology, Dr. Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[h] Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[i] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[j] Department of Endocrinology, Skull Base Research Center of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[k] ENT and Head and Neck Research Center and Department, The Five Senses Health Institute, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[l] Radiation Oncology Department, Iran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Objective: Predicting postoperative persistence and recurrence of Cushing's disease (CD) remains a clinical challenge, with no universally reliable models available. This study introduces the CuPeR model, an online dynamic nomogram developed to address these gaps by predicting postoperative outcomes in patients with CD undergoing pituitary surgery.

Methods: A retrospective cohort of [illegible] patients treated for CD between [illegible] and [illegible] was analyzed. Key patient and tumor characteristics, imaging findings, and treatment details were evaluated. Multivariate logistic regression identified independent predictors of postoperative persistence or recurrence of CD (PeRP-CD), which were then incorporated into the CuPeR model using stepwise selection based on Akaike Information Criterion. Internal validation was performed using a testing dataset, and a user-friendly online nomogram was developed to facilitate immediate, patient-specific risk estimation in clinical practice.

Results: The final predictive model identified four key factors: symptom duration, MRI Hardy's grade, tumor size, and prior pituitary surgery. Longer symptom duration and a history of prior surgery significantly increased the risk of recurrence, while bilateral tumor location reduced this risk. The model demonstrated an area under the receiver operating characteristic curve (AUC-ROC) of 0.7[illegible], with 8[illegible]% accuracy, specificity of [illegible], and sensitivity of [illegible].

Conclusion: The CuPeR model may offer a practical tool for predicting PeRP-CD, enhancing postoperative decision-making by providing personalized risk assessments.

Abbreviations: ACTH, Adrenocorticotropic Hormone; AIC, Akaike Information Criterion; AUC, Area Under the Curve; BMI, Body Mass Index; CD, Cushing's Disease; CI, Confidence Interval; CRH, Corticotropin-Releasing Hormone; DFS, Disease-Free Survival; DL, Deep Learning; eTSS, Endoscopic Transsphenoidal Surgery; HR, Hazard Ratio; IPSS, Inferior Petrosal Sinus Sampling; ML, Machine Learning; MRI, Magnetic Resonance Imaging; OS, Overall Survival; PeRP-CD, Persistent or Recurrent Cushing's Disease; SIADH, Syndrome of Inappropriate Antidiuretic Hormone Secretion; TSS, Transsphenoidal Surgery; UFC, Urinary Free Cortisol.

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* Corresponding author at: ENT and Head and Neck Research Center and Department, The Five Senses Health Institute, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

** Corresponding author at: Skull Base Research Center, Loghman Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

E-mail addresses: [illegible] (S.A. Mousavinejad), [illegible] (F. Taghizadeh-Hesary).

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Introduction

Cushing's disease (CD) is a rare endocrine disorder, with an annual incidence rate of approximately 2.24 cases per 100,000 individuals [1]. Transsphenoidal surgery (TSS), performed using either endoscopic or microscopic approaches, remains the cornerstone of treatment for CD. Notably, meta-analytical studies have reported that TSS achieves remission and provides long-term disease control in 71–80 % of patients [2–4]. The remaining cases may experience persistent disease despite surgery, while others may face disease recurrence despite initial remission. In such cases, additional treatment options include second pituitary surgery, pituitary irradiation, targeted medical therapies, and bilateral adrenalectomy, each with varying success rates ranging from 25 % for medical therapy to 100 % for bilateral adrenalectomy [5].

To date, no single predictive factor has proven effective in reliably forecasting treatment outcomes in patients with CD [4]. This underscores the critical need for developing predictive models to assess the likelihood of postoperative recurrence or persistence of Cushing's disease (PoRP-CD). However, only a limited number of studies have addressed this gap. Notably, two studies from Peking Union Medical College Hospital attempted to tackle this issue using machine learning (ML) and deep learning (DL) approaches [6,7]. These studies utilized demographic, clinical, and paraclinical variables to construct predictive models, with DL approaches showing potential to enhance predictive accuracy [7]. While the results of these models were promising, their applicability in routine clinical practice remains limited. Both studies focused exclusively on patients undergoing their initial transsphenoidal surgery, making them less applicable for cases involving patients with a prior history of pituitary surgery or radiotherapy. Furthermore, these models incorporated both preoperative and postoperative parameters, such as changes in cortisol and adrenocorticotropic hormone (ACTH) levels. However, serum cortisol, ACTH, and comprehensive endocrine testing should be available before any treatment decisions are made, and each patient should ideally be reviewed by a multidisciplinary tumor board, including neurosurgery, radiology, endocrinology, and oncology, prior to pituitary surgery. As such, more comprehensive and practical predictive tool that can support timely clinical decision-making and accommodate a broader range of patient scenarios in the management of CD.

The current study was designed to address these critical limitations and provide a more practical solution for predicting postoperative outcomes in CD. Applying one of the largest available CD cohorts, we incorporated a wide array of patient and tumor characteristics, imaging findings, and treatment details to develop a robust and comprehensive predictive model. This model offers treating surgeons reliable insights into the likelihood of tumor recurrence or persistence. By providing individualized risk predictions, the model is intended to assist clinicians in considering different therapeutic options before pituitary surgery, complementing—but not replacing—standard multidisciplinary decision-making. To further enhance its utility in clinical practice, we also developed an interactive online dynamic nomogram, allowing individualized predictions of postoperative persistence or recurrence.

Methods

Study design, patients, and endpoints

The experimental protocol was approved by the Institutional Review Board of Shahid Beheshti University of Medical Sciences (Tehran, Iran). This retrospective study investigates the clinical outcomes of pituitary surgery in patients with CD underwent pituitary surgery between 2010 and 2024 in the neurosurgery department at Loghman Hakim Hospital. Surgeries were conducted by a group of experienced neurosurgeons under the supervision of the first author (H.S). The primary objective of this study was to develop and validate a predictive model for assessing the risk of PoRP-CD. The secondary objectives were (a) to summarize patient and tumor characteristics, (b) to report surgical outcomes and remission rates following surgery, and (c) to analyze patient survival. This study was performed in accordance with the Declaration of Helsinki, and adheres to the reporting guidelines outlined in the STROBE Statement. Due to retrospective nature of the study informed consent was waived by Shahid Beheshti University of Medical Sciences Ethics Committee. All methods were performed in accordance with the relevant guidelines and regulations.

Preoperative assessments

The "index surgery" was set to the most recent pituitary surgery. Before the index surgery, patients underwent comprehensive clinical evaluations, including biochemical and neurological assessments as well as visual field examinations. This research utilized the Endocrine Society Clinical Practice Guideline to establish the diagnosis of CD [8]. Three main steps were involved in the diagnostic process: in the first step, the focus was on detecting hypercortisolemia, which was determined by examining 24-hour urinary free cortisol levels (normal: <60 mcg/24 h), as well as plasma and salivary cortisol profiles. Low-dose dexamethasone suppression testing was performed using the 2 mg/48 h protocol, which was the standard practice in our institution during the study period (2010 onward) [8]. The second step aimed to confirm ACTH-dependent cases of hypercortisolemia, through measuring plasma ACTH levels. The final step aimed to distinguish Cushing's disease from ectopic sources of ACTH. This was performed using a high-dose dexamethasone suppression test (8 mg overnight), with a plasma cortisol suppression exceeding 50 % typically considered indicative of a pituitary origin [8].

Next, the patients were subjected to thin-slice (2 mm) 1.5-tesla dynamic pituitary gland magnetic resonance imaging (MRI) with gadolinium contrast. The MR evaluation adhered to a strict protocol, requiring an independent agreement of treating neurosurgeon and radiologist to confirm the diagnosis. MR scans were categorized according to the Hardy and Knosp classifications [9,10]. Normal scans required to demonstrate the absence of direct signs, including inhomogeneity in the pituitary, as well as indirect signs such as a deviation of the pituitary stalk, bulging or erosion of the Sella contour. In cases where the CD was confirmed but pituitary MRI was inconclusive, bilateral inferior petrosal sinus sampling (IPSS) was performed per standard protocol under corticotropin-releasing hormone (CRH) stimulation [11]. Patients with macroadenoma or signs of elevating the optic chiasm were candidates for Humphrey visual field examination.

Surgical approach

Patients underwent endoscopic transsphenoidal approach using conventional "Two Nostrils-Four Hands" technique [12]. Given the diminutive size and deep-seated location of most adenomas, locating the adenoma amongst as a formidable challenge, particularly when the tumor remained not visualized in pre-operative imaging studies. The surgical procedure entailed extensive drilling of the Sellar floor laterally to the internal artery on both sides, providing a comprehensive view of the medial wall of the cavernous sinus and exposure of the anterior and posterior intercavernous sinuses. The exploration of the entire Sella commenced in the region where the original tumor had been localized. Upon identification of a tumor, a selective adenomectomy was performed, accompanied by a thorough inspection of the pituitary gland to detect and eliminate any potential tumor remnants. The removal of any pseudo capsule was executed meticulously.

The primary surgical objective was selective adenomectomy, with further exploration guided by the side recommended by IPSS in cases where no adenoma was initially observed. The exploration involved making a pin-like incision on the corresponding half of the gland, enabling deep exploration to leave no part unexplored. In instances where creamy material suggestive of a tumor was drained after a

pituitary incision, a tissue biopsy was obtained, although it was not conclusively considered a tumor. Exploration continued on the opposite side in such cases.

When no distinct adenoma was found, a peri-glandular inspection was conducted to visualize the medial wall of the cavernous sinus, diaphragm, and Sellar floor, aiming to detect an ectopic microadenoma. If an apparent tumor remained undetected, the procedure was repeated on the contralateral side, and a vertical medial incision on the pituitary gland adjacent to the pituitary stalk and neurohypophysis was made as a final effort for tumor detection. In the absence of identified pathology during the surgical procedure, hemi-hypophysectomy was considered on the side where IPSS had detected the gradient or on the side with an apparent or suspicious MRI finding. Considering the typical central location of corticotroph cells in the pituitary gland, microadenoma exploration extended posteriorly and medially to confirm extirpation.

Postoperative assessments

In this study, the patients were closely monitored for signs of diabetes insipidus and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Serum sodium levels, urine-specific gravity, and volume were checked regularly. Following surgery, morning cortisol levels were measured on the first day, and other anterior pituitary hormones were evaluated on day 3. Hydrocortisone therapy was initiated based on the patient's symptoms, signs of adrenal insufficiency, and low cortisol levels. The first postoperative check-up occurred two weeks after surgery, followed by another at three months, which included a comprehensive assessment of pituitary hormones. This evaluation was repeated every three months for two years and then annually. Additionally, patients underwent a dynamic 1.5-Tesla pituitary MRI at six months post-surgery and annually thereafter, with a minimum follow-up period of 12 months.

Remission was defined as having low cortisol levels, indicated by early morning serum cortisol level ≤ 5 μg/dL within two days post-surgery [18]. Persistent CD was characterized by ongoing hypercortisolism, and postoperative recurrence refers to the reappearance of CD symptoms despite initial remission marked by hypocortisolemia. In case of persistence or recurrence, patients were candidates for second-line treatment options selected by their physicians, including revision surgery, targeted medical therapy, pituitary radiotherapy, or bilateral adrenalectomy. Disease-free survival (DFS) was defined as the time from the index surgery to the first occurrence of disease recurrence or death from any cause, while overall survival (OS) was defined as the time from the index surgery to death from any cause.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as mean, range, and standard deviation. The distribution of variables was checked using the Shapiro-Wilk test, which showed a deviation from normal distribution. Contingency tables were used for categorical variables with Pearson's Chi-squared or Fisher's Exact test used to examine their association with outcomes for univariate analyses. For continuous variables, the unpaired t-test was applied to compare means between two independent groups when the data met the assumption of normality. Analyses were conducted with R Statistical Software v4.4.0 ("Puppy Cup"). All statistical inferences were two-sided, and $P < 0.05$ were considered statistically significant.

Model development and internal validation

The dataset was split by "caret package" into a training set (70 %) and a testing set (30 %) using stratified sampling to ensure representative proportions of outcomes. Binary logistic regression was used to identify predictors of PoRP-CD. Patients with adequate follow-up data were included in the analysis. The variables with a marginal level of association ($P < 0.15$) in the univariate analysis were further included in the multivariate logistic regression analysis to identify the independent predictors of PoRP-CD. Imputed factors included demographics, medical history, imaging and pathology results, and treatment details. To identify predictors of PoRP-CD, a multivariable logistic regression model was developed using stepwise selection based on Akaike Information Criterion (AIC). Model performance, including sensitivity, specificity, and area under the receiver operating characteristic curve (AUC-ROC), was evaluated using internal validation on the test dataset.

Nomogram creation and deployment

A nomogram was constructed using the validated logistic regression model. The nomogram was then integrated into a web-based application using the "Shiny package" in R program. The dynamic nomogram allows clinicians to input patient data and obtain individualized risk predictions for PoRP-CD.

Survival analysis

Survival analysis was conducted to evaluate DFS across various patient subgroups. The log-rank test was applied to assess statistical differences in survival distributions between subgroups. Cox proportional hazard regression was used to estimate hazard ratios (HR) and 95 % confidence intervals (CI). The "survival" and "survminer" R packages were applied in this section.

Results

Patients and tumors characteristics

A total of 211 patients with CD had been treated by a group of experienced neurosurgeons under the supervision of the first author (G. S) between March 2010 and January 2024 in the neurosurgery department at Loghman Hakim Hospital. Table 1 summarizes the baseline characteristics of patients at the timepoint of index surgery. The patients had a mean age of 33.9 ± 12.1 years (range: 11–67), among which 21 patients (9.9 %) were in the pediatric age range, and 165 (78.1 %) were female. Obesity was the most common patients' symptoms (40.9 %), and physical examination reported centripetal obesity (64.3 %), moon face (75.8 %), and striae (54.4 %) as the most common clinical manifestations. Compared to the adult patients, pediatrics had less common hypertension on physical examination (38.2 vs. 9.0 %) and medical history of diabetes mellitus (26.6 vs. 4.7 %) ($P < 0.05$). The majority of patients (63.9 %, 135/211) had not received any prior treatment. Among those who had, surgery alone was the most common approach (n = 57, 27.0 %), performed once in 50 patients (23.6 %), twice in 6 patients (2.8 %), and three times in a single patient.

A comprehensive preoperative hormonal assessment was conducted on 77 patients (36.4 %), revealing hormonal dysregulation in 28 patients (36.3 %). Hypothyroidism was the most common abnormality, affecting 31 % of those assessed (24 out of 77). On MRI scans, most tumors were microadenomas (58.6 %), with fewer macroadenomas (24.3 %) and some cases with no detectable tumor (17.3 %). Tumors were commonly localized bilaterally (36.3 %) or centrally (34.7 %), and most were unifocal (80.1 %). Knosp grading indicated no cavernous sinus invasion in the majority (32.6 %), with only 8.4 % showing grades 3–4. According to Hardy's grading, most patients had mild sphenoid bone invasion, predominantly grade I (58.2 %). For Hardy's staging of suprasellar extension, nearly half were at stage B (48.8 %), with smaller groups in stages A and E (20.4 % each), and fewer in stages C and D. Other MRI findings are summarized in Table 1. There was no significant difference between adult and pediatric patients in terms of hormonal and imaging findings ($P > 0.05$). Pathology reports were available for 36 patients. The most common finding was sparse cellularity, observed in 11 patients (30.6 %) followed by dense cellularity identified in 9 patients (25 %). Crooke cell changes were the least common, present in 7 patients (19.4 %). Nine specimens (25 %) had no tumor identified in the sample submitted to pathology.

Table 1
Baseline characteristics of adult and pediatric patients with Cushing's disease.

Demographics	Total n = 211	Adults n = 190	Pediatrics n = 21	P	Medical Hx	Total n = 211	Adults n = 190	Ped. n = 21	P	Drug-Family Hx	Total n = 211	Adults n = 190	Ped. n = 21	P
Age, mean±SD (y)	36.9±13.1	38.3±12.2	14.8±1.7	<0.001	Hypertension	97 (46.0)	92 (48.4)	5 (23.8)	0.21	Cabergoline	3 (1.4)	3 (1.5)	0	1.0
Sex, female	165 (78.1)[a]	149 (78.4)	16 (76.2)	0.78	Diabetes mellitus	71 (33.6)	70 (36.8)	1 (4.7)	<0.001	Ketoconazole	12 (5.6)	12 (6.3)	0	0.61
Marital status, married	158 (75.0)[b]	155 (75.8)[b]	3 (13.3)[b]	<0.001	Dyslipidemia	46 (21.8)	42 (22.1)	3 (14.2)	0.36	Metyrapone	0	–	–	–
Smoking status: active/passive/none	17 (8.0)/27(12.7)/112(73)[b]	17 (9.1)/23(12)/100(70)[b]	0/4(20)/12(78)[b]	0.73	Prior pituitary surgery	57 (27.0)	51 (26.8)	6 (28.5)	1.0	Pasireotide	0	–	–	–
Height, mean±SD (cm)	159.9±8.7	160.6±8.6	153.1±8.8	0.39	Sleep apnea	37 (17.5)	32 (16.8)	5 (23.8)	0.36	Somatostatin	0	–	–	–
Weight, mean±SD (kg)	74.1±22.5	74.6±22.5	68.2±21.1	0.58	Thromboembolism	6 (2.8)	6 (3.1)	0	1.0					
BMI, mean±SD (kg/m²)	28.8±6.1	29.2±6.2	27.8±5.8	0.72	DVT	3 (1.4)	3 (1.5)	0	1.0	FH of Cushing	5 (2.3)	4 (2.1)	1 (4.7)	0.46
Symptom duration, mean±SD (m)	30.7±41.2	31.5±43.1	20.2±14.2	0.78	MEN	1 (0.4)	1 (0.5)	0	1.0	FH of MEN	1 (0.4)	1 (0.5)	0	1.0
Presenting Symptoms														
Obesity	78 (36.9)[a]	65 (34.2)[a]	6 (28.5)[a]	0.61	Delay	10 (5.1)[a]	8 (3.4)[a]	2 (11.7)	0.27	Headache	4 (1.4)[a]	3 (1.0)[a]	1 (5.5)	0.39
Abnormal menstruation	16 (8.8)[a]	12 (6.8)[a]	3 (17.6)[a]	0.22	Edema	7 (4.2)[a]	7 (4.7)[a]	0	1.0	Diabetes mellitus	3 (1.8)[a]	3 (2.0)[a]	0	1.0
Hypertension	16 (7.8)[a]	12 (6.3)[a]	0	0.61	Muscular weakness	7 (4.2)[a]	6 (4.1)[a]	1 (5.8)	0.34	Bone fractures	3 (1.8)[a]	3 (2.0)[a]	0	1.0
Blurred vision	10 (6.1)[a]	9 (6.0)[a]	1 (5.8)[a]	1.0	Moon face	6 (3.6)[a]	6 (4.1)[a]	0	1.0	Other	10 (6.1)	10 (6.8)	0	0.60
Clinical Manifestations														
Abdominal striae	35 (16.5)	34 (17.8)	1 (4.7)	0.13	Easy bruising	102 (48.3)	92 (48.4)	11 (52.3)	0.81	Hair gain/hair loss	111 (52.6)	100 (52.6)	11 (52.3)	1.0
Acne	68 (32.2)	58 (30.5)	10 (47.6)	0.18	Ecchymosis	58 (27.5)	50 (26.3)	8 (38.0)	0.27	Hyperandrogenism	96 (45.4)	84 (44.2)	12 (57.1)	0.46
Ankle edema	105 (49.7)	96 (50.5)	9 (42.8)	0.87	Exophthalmos	50 (23.7)	47 (24.7)	3 (14.2)	0.37	Moon face	160 (75.8)	141 (74.2)	19 (90.4)	0.66
Backache	66 (31.2)	60 (31.5)	6 (28.5)	0.88	Facial plethora	97 (45.9)	85 (44.7)	12 (57.1)	0.35	Osteoporosis	25 (11.8)	25 (13.2)	0	0.14
Blurred vision	70 (33.2)	67 (35.2)	3 (14.2)	0.27	Fatigue	146 (69.2)	130 (68)	16 (76.1)	0.70	Proximal myopathy	94 (44.5)	86 (45.2)	8 (38.0)	0.82
Buffalo hump	123 (58.2)	107 (56.3)	16 (76.1)	0.42	Fracture	11 (5.2)	11 (5.8)	0	0.61	Skin atrophy	81 (38.4)	73 (38.4)	8 (38.0)	1.0
Centripetal obesity	178 (84.3)	159 (83.6)	19 (90.4)	0.30	Headache	109 (51.6)	97 (51.0)	12 (57.1)	1.0	Striae	136 (64.4)	119 (62.6)	17 (80.9)	0.66
Cerebrospinal fluid leakage	5 (2.3)	4 (2.1)	1 (4.7)	0.41	Hirsutism	104 (49.2)	92 (48.4)	12 (57.1)	0.72	Supraclavicular fat pad	38 (18.0)	33 (17.3)	5 (23.8)	0.57
Cranial nerve palsy	3 (1.4)	3 (1.5)	0	1.0	Hyperpigmentation	38 (18.0)	37 (19.4)	1 (4.7)	0.12	Visual field defect	24 (11.3)	22 (11.5)	2 (9.5)	1.0
Diplopia	18 (8.5)	15 (7.8)	3 (14.2)	0.41	Hypokalemia	69 (32.7)	67 (35.2)	2 (9.5)	0.028	Weight gain	108 (51.1)	95 (50.0)	13 (61.9)	0.39
Prior Treatment														
Treatment naive	180 (84.9)	162 (84.2)	18 (85.7)	1.0	Pituitary surgery alone	39 (18.4)	33 (17.3)	6 (28.5)	0.23	Radiotherapy alone	6 (2.8)	5 (2.6)	1 (4.7)	0.47
Medication alone	5 (2.3)	5 (2.6)	0	1.0	Combination therapy	17 (8.0)	17 (8.9)	0	0.22	Adrenalectomy alone	11 (5.2)	10 (5.2)	1 (4.7)	1.0
Hormonal Assessments														
Hypothyroidism	24 (11.3)[b]	24 (12.6)[c]	0	0.09	GH deficiency	6 (2.8)[b]	6 (3.1)[c]	0	1.0	Hypogonadism	7 (3.3)[b]	7 (3.6)[c]	0	1.0
Panhypopituitarism	2 (0.9)[b]	2 (1.0)[b]	0	1.0										
Imaging Features														

(continued on next page)

Table 1 (continued)

Demographics	Total n = 211	Adults n = 190	Pediatrics n = 21	P
Hardy's grading (sphenoid bone invasion)				0.48
0	37 (21.1) [b]	35 (22.7) [b]	2 (9.5)	
1	101 (58.3) [b]	88 (57.1) [b]	14 (66.7)	
2	27 (15.4) [b]	22 (14.3) [b]	4 (19.0)	
3	4 (2.3) [b]	3 (1.9) [b]	1 (4.7)	
4	5 (2.8) [b]	5 (3.2) [b]	0	
Tumor size				0.28
Microadenoma	122 (58.8) [b]	111 (59.3) [b]	11 (52.4)	
Macroadenoma	50 (24.2) [b]	42 (22.4) [b]	8 (38.1)	
MRI-negative	36 (17.3) [b]	34 (18.1) [b]	2 (9.5)	
Invasion [c]				1.0
No invasion	188 (88.6) [b]	168 (87.7) [b]	20 (95.2) [b]	
Cavernous sinus	12 (5.7) [b]	11 (5.8) [b]	1 (4.8) [b]	
Carotid	3 (1.4) [b]	3 (1.6) [b]	0	
Dura	6 (2.8) [b]	6 (3.1) [b]	0	
Clivus	3 (1.4) [b]	3 (1.6) [b]	0	
Pituitary apoplexy				0.08
No	198 (97.2) [b]	187 (98.3) [b]	19 (90.5) [b]	
Yes	5 (2.8) [b]	3 (1.7) [b]	2 (10.5) [b]	

Medical Hx	Total n = 211	Adults n = 190	Ped. n = 21	P
Hardy's staging (suprasellar extension)				0.07
A	36 (20.4) [b]	34 (21.8) [b]	2 (9.5)	
B	86 (48.9) [b]	73 (47.1) [b]	13 (62)	
C	14 (7.9) [b]	14 (9.0) [b]	0	
D	4 (2.3) [b]	2 (1.3) [b]	2 (9.5)	
E	36 (20.4) [b]	32 (20.6) [b]	4 (19.0)	
Sphenoid stage				1.0
Sellar	206 (97.6) [b]	184 (97.3) [b]	21 (100)	
Presellar	3 (1.4) [b]	3 (1.6) [b]	0	
Conchal	2 (0.9) [b]	2 (1.0) [b]	0	
Tumor site				0.26
Right lobe	22 (10.6) [b]	20 (10.2) [b]	2 (11.1) [b]	
Left lobe	16 (11.3) [b]	13 (10.5) [b]	3 (16.6) [b]	
Bilateral	51 (28.1) [b]	43 (24.9) [b]	8 (44.4) [b]	
Central	46 (24.7) [b]	42 (26.5) [b]	4 (22.2) [b]	
Stalk	3 (2.1) [b]	2 (1.6) [b]	1 (5.5) [b]	
Kissing carotids				1.0
No	209 (99.1)	188 (98.9)	21 (100)	
Yes	2 (0.9)	2 (1.0)	0	

Drug-Family Hx	Total n = 211	Adults n = 190	Ped. n = 21	P
Knosp grading				0.48
0	132 (62.6) [b]	115 (60.5) [b]	17 (81.0)	
1	15 (7.1) [b]	20 (10.5) [b]	3 (14.3)	
2	7 (3.3) [b]	8 (4.2) [b]	1 (4.7)	
3	4 (2.1) [b]	4 (2.4) [b]	0	
4	8 (4.2) [b]	8 (4.2) [b]	0	
Multifocality				0.78
Unifocal	113 (80.1)	97 (79.5)	16 (84.2)	
Multifocal	28 (19.8)	25 (20.4)	3 (15.7)	
Empty sella				0.54
No	207 (98.1)	187 (98.4)	20 (95.2)	
Yes	4 (1.8)	3 (1.5)	1 (4.7)	

[a] the numbers in parentheses represent the percentage for each patient group.

[b] percentage after ruling out missing data.

[c] one patient had invasion to cavernous sinus and carotid and another one had clivus and dural invasion.

Treatment details and outcomes

A total of 58 patients (17.1 %) underwent postoperative DFSI, among which 13 had right lateralization, 12 left, 4 bilateral, 3 central, 2 central-right, and 1 central-left. Pituitary surgery was predominantly performed using the endoscopic transsphenoidal (eTSS) approach (99.3 %, 338/341), while the sublabium approach was used in 2 patients (0.7 %). Adenomectomy was the most common surgical procedure (n = 197, 58.4 %), followed by total hypophysectomy in 17 patients (5.1 %) and hemi-hypophysectomy in 7 patients (2.3 %). In addition, four patients in the total hypophysectomy group and one patient in the adenomectomy group also underwent hypophyseal stalk resection. Information on disease persistence or recurrence was available for 204 patients. Median follow-up of patients was 38.4 months (range: 4.8–170.4 months) after index surgery. In total, 23 patients (11.2 %) experienced persistent disease following the index surgery, while 10 patients (4.9 %) had disease recurrence, with a median time to recurrence of 7 months (range: 1–78 months). The median recurrence-free interval for the entire cohort was 27 months.

The surgical complication rates were as follows (Fig. 1A): cerebrospinal fluid leaks were observed in 22 patients (13.4 %), followed by cranial nerve injury in 7 patients (2.3 %) and meningitis in 5 patients (1.2 %). Carotid injury and intracerebral bleeding each occurred in 2 patients (1.4 %). Nasal bleeding, the need for a ventriculoperitoneal shunt, and embolic events were each reported in 1 patient (0.4 %). Perioperative mortality was observed in one female patient (0.4 %) due to an iatrogenic carotid injury. This patient had previously undergone three pituitary surgeries and received radiotherapy at the pituitary site. Hormonal dysregulations following surgery included hypothyroidism in 99 patients (46.9 %), diabetes insipidus in 76 patients (36 %), hypogonadism in 28 patients (13.3 %), growth hormone deficiency in 10 patients (4.7 %), and panhypopituitarism in 7 patients (3.3 %) (Fig. 1B).

Multivariable analysis on the predictors of Persistent/Recurrent Cushing's disease

To identify potential predictive factors for PeRP-CD, we conducted a comprehensive binary logistic regression analysis, examining key clinical and imaging variables (Table 2). In the univariate analysis, factors including symptom duration (OR [odds ratio] 1.01, 95 % CI [confidence interval] 1.00–1.03, $P = 0.04$), MRI Hardy's grade (OR 1.65, 95 % CI 0.99–2.69, $P = 0.05$), and previous pituitary surgery (OR 3.56, 95 % CI 1.34–8.87, $P = 0.007$) demonstrated significant association with PeRP-CD. MRI-reported tumor size showed increased odds of recurrence with an increased tumor size (OR for microadenoma vs. no tumor: 2.41, 95 % CI: 0.50–41.53), OR for macroadenoma vs. no tumor: 4.18, 95 % CI 0.88–21.42), though the effect was not statistically significant ($P > 0.05$). To include missing the marginal significant factors, those factors with P values between 0.05 and 0.15 were also included in the multivariate analysis, including "MRI Knosp grading", "MRI-reported tumor size", and "previous pituitary radiotherapy". In the multivariate analysis, "symptom duration" was positively correlated with recurrence, with an odds ratio (OR) of 1.02 (95 % CI: 1.00–1.04, $P = 0.04$), indicating a higher risk of recurrence with prolonged symptoms. Additionally, a history of "previous pituitary surgery" was significantly associated with recurrence, with an OR of 4.47 (95 % CI: 1.04–20.59, $P = 0.04$). Other factors, including tumor grading, tumor size, and previous radiotherapy, did not reach statistical significance.

The stepwise selection-in both forward and backward directions-retained four predictors— symptom duration, Hardy's grading, tumor size, and prior surgery —for the final model. The final multivariate model with four predictors of "symptom duration", "MRI Hardy's grading", "tumor size", and "previous pituitary surgery" demonstrated significant associations for "symptom duration" (OR 1.03, 95 % CI: 1.005–1.05, $P = 0.01$), previous pituitary surgery (OR 4.61, 95 % CI: 1.13–32.0, $P = 0.03$), and a certain tumor size, tumors located bilaterally had significantly lower odds of recurrence compared to central tumors (OR 0.01, 95 % CI: 0.0002–0.48, $P = 0.02$). On the testing dataset, the four-factor model achieved an AUC of 0.72, specificity of 96 %, and sensitivity of 33 %. The model's accuracy in predicting PeRP-CD is 89 %.

Predicting persistent or recurrent Cushing's disease—The CuPeR nomogram

A nomogram was developed based on the multivariable model comprising four key predictors: "Symptom duration", "MRI-Hardy's grading", "Previous pituitary surgery", and "MRI-reported tumor size" (Fig. 2). This nomogram visually represents the impact of each predictor on the likelihood of PeRP-CD. The total score derived from the nomogram aligns with the probability scales, allowing for estimation of the risk of PeRP-CD. Higher cumulative points correspond to an increased likelihood of persistent or recurrent disease. To facilitate individualized predictions of postoperative persistence or recurrence, we developed an online dynamic nomogram (link: https://xueheng.shinyapps.io/cuper/).

Survival analysis

Survival analysis demonstrated a steady, gradual decline in DFS across the entire cohort, with the median DFS not reached despite substantial follow-up (Fig. 3A). Among the predefined variables, Hardy's Grade 3 was associated with a significantly worse DFS compared with Grade 0 (HR = 6.02, 95 % CI: 1.06–33.60, $P = 0.03$) (Fig. 3B), whereas other Hardy's Grades did not reach statistical significance ($P > 0.05$). Regarding tumor size, no size was a statistically significant risk factor for DFS; male tumors showed a trend toward greater DFS but did not reach significance (HR = 3.09, 95 % CI: 0.84–33.63, $P = 0.07$) (Fig. 3C). Patients with a history of previous pituitary surgery had significantly worse DFS (HR = 4.72, 95 % CI: 2.29–9.73, $P < 0.01$) (Fig. 3D). In contrast, symptom duration was not associated with poor DFS (HR = 1.26, 95 % CI: 0.86–2.81, $P = 0.57$) (Fig. 3E). A similar analysis on OS was not performed, as only five events were recorded among the 211 patients (2.36 %), rendering meaningful statistical analysis infeasible.

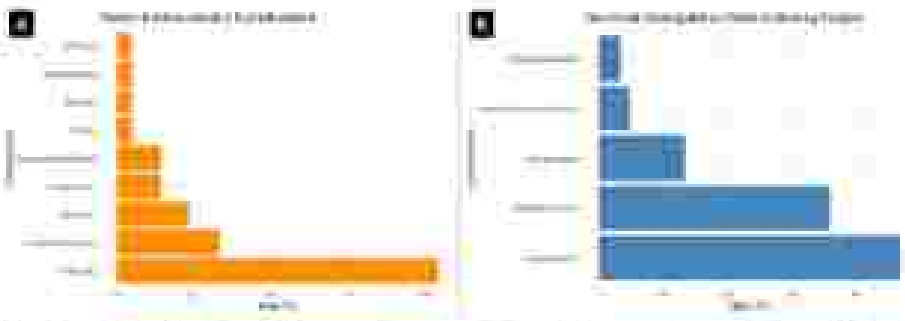

Fig. 1. Rates of surgical complications. (a) Intraoperative complications; (b) hormonal dysregulation rates following surgery.

Table 2
Regression analysis of patient and tumor's factors related to postoperative persistence or recurrence in Cushing disease.

Parameters	Univariate Analysis		Multivariate Analysis	
	OR (95 % CI)	P	OR (95 % CI)	P
Age	0.97 (0.94–1.01)	0.20		
Sex (male vs. female)	1.17 (0.39–3.50)	0.77		
Smoking (active smoking vs. none)	0.76 (0.05–10.00)	0.77		
Family history of CD (positive vs. negative)	0.01 (0-Inf)	0.99		
Family history of MEN (positive vs. negative)	0.01 (0-Inf)	0.99		
Preoperative BMI	1.02 (0.94–1.10)	0.48		
Symptom duration	1.01 (1.00–1.02)	0.04 **	1.02 (1.01–1.03)	0.01 **
Preop serum ACTH (high vs. normal)	0.88 (0.18–4.30)	0.90		
Preop free serum cortisol (high vs. normal)	1.18 (0.40–3.48)	0.76		
Preop urine free cortisol (high vs. normal)	0.23 (0.01–2.88)	0.20		
Knosp grading (≥3 vs. grade 3)	1.41 (0.96–2.10)	0.08 *	1.38 (0.81–2.37)	0.24
Hardy's grading (≥3 vs. grade 3)	1.62 (0.96–2.69)	0.03 **	1.96 (0.54–7.21)	0.29
Hardy's staging (≥3 vs. stage 4)	3.87 (1.01–14.88)	0.17		
Tumor size		0.17		
Macro vs. no tumor Micro vs. no tumor	4.13 (0.80–21.40) 2.41 (0.50–11.66)			
Multifocality (multifocal vs. unifocal)	1.68 (0.44–6.42)	0.44		
MRI-based tumor site[a]		0.14 *		
Bilateral vs. central Left vs. central Right vs. central Both vs. central	0.18 (0.02–1.58) 0.82 (0.16–4.40) 0.40 (0.06–2.82) 5.20 (0.27–144.18)		0.24 (0.02–2.30) 2.22 (0.55–8.12) 5.26 (0.19–148.28) (0.0002–0.07)	0.02 ** 0.28 0.27 0.21
Invasion (pos. vs. neg.)	1.16 (0.21–4.81)	0.80		
Surgical approach (transplanum vs. eTSS)	6.22 (0.27–103.83)	0.30		
Surgical type (adenomectomy vs. hypophysectomy)	1.28 (0.46–3.26)	0.60		
Histopathology		0.58		
Dense type vs. Crooke's cell adenoma Unusual appearing vs. Crooke's cell adenoma Sparse type vs. Crooke's cell adenoma	3.00 (0.19–48.00) 5.80 (0.54–28.13) 0.28 (0.01–6.45)			
Ki-67 (≥3% vs. < 3 %)	1.24 (0.14–10.84)	0.79		
Previous pituitary surgery (yes vs. no)	3.06 (1.39–6.07)	0.005 **	4.87 (1.04–20.88)	0.04 **
Previous pituitary radiotherapy (yes vs. no)	2.26 (0.89–11.62)	0.07 *	2.65 (0.26–48.07)	0.21
Postop decrease in BMI	0.90 (0.78–1.08)	0.22		

Abbreviations: ACTH – Adrenocorticotropic Hormone; BMI – Body Mass Index; CD – Cushing's Disease; CI – Confidence Interval; eTSS – Endoscopic Transsphenoidal Surgery; Inf – Infinity; MEN – Multiple Endocrine Neoplasia; MR – Magnetic Resonance; OR – Odds Ratio; PeRP-CD – Persistent or Recurrent Cushing's Disease; Preop – Preoperative; Postop – Postoperative.
[a] MR-reported.
* Significant at the level of 0.15.
** Significant at the level of 0.05.

Discussion

In this large cohort study, we developed the CaPeR model, a comprehensive predictive tool for PeRP-CD, by analyzing diverse patient and tumor characteristics, imaging findings, and treatment details. This model identified four key predictors—symptom duration, MRI Hardy's grade, tumor site, and previous pituitary surgery. Multivariate analysis revealed that longer symptom duration and a history of prior surgery significantly increased recurrence risk, while bilateral tumor location was associated with a reduced risk. Validated with an AUC of 0.70 and 83 % accuracy on the testing dataset, the model offers significant clinical utility by providing treating surgeons with valuable insights into postoperative outcomes.

This study is among the few to develop a predictive model for estimating PeRP-CD (Table 3). Previous efforts, such as those by Liu et al. [6] and Fan et al. [7], employed machine learning and deep learning methodologies, respectively, demonstrating promising results (AUCs of 0.78 and 0.84). However, both studies were limited in their applicability to many clinical settings, as they focused solely on patients undergoing initial surgeries and incorporated postoperative parameters, which are unavailable for preoperative decision-making. By addressing these gaps, our study contributes a more practical tool for use in diverse clinical scenarios. Moreover, the findings of this study align with predictors identified in prior research. For instance, factors such duration of symptoms and history of previous pituitary surgery have been highlighted as critical for recurrence [5,14]. Importantly, our inclusion of MRI-based predictors and preoperative variables ensures the model's relevance during preoperative planning, distinguishing it from previous approaches.

Several other studies aimed to explore the predictive value of single predictors. Braun et al. (2020) summarized the predictors for CD remission following TSS in a systematic review. Key predictors include pre-surgical identification of the tumor via MRI and the absence of adenoma invasion into the cavernous sinus. Postoperative hormonal levels, particularly low cortisol (< 2 μg/dL) and ACTH levels (< 3.3 pmol/L) as well as low cortisol levels (< 35 nmol/L) at 6–12 weeks post-surgery and sustained hypocortisolism requiring long-term replacement therapy, were significant indicators of remission. Additionally, post-surgical decreases in BMI contributed to favorable outcomes. Other reported predictors included a high level of surgical expertise, younger patient age, non-mutant USP8 corticotroph tumors, and swift recovery from postoperative adrenal insufficiency [3].

This study has certain limitations that should be acknowledged. The reliance on retrospective data may result in potential biases in variable selection and data completeness. While the model demonstrated good predictive accuracy, its limited sensitivity may restrict its ability to identify all high-risk patients. Moreover, the model has not been externally validated in independent cohorts, which limits its generalizability to other clinical settings. Despite these limitations, the study possesses significant strengths that underscore its contribution to the field. Applying one of the largest CD cohorts, it provides a robust statistical foundation and enhances the reliability of the findings. The comprehensive inclusion of diverse patient and tumor characteristics, imaging findings, and treatment details resulted in a clinically relevant and well-rounded prediction model. Notably, this model stands out for its applicability to a broader spectrum of patients, including those with prior surgeries or radiotherapy, addressing a gap left by earlier studies.

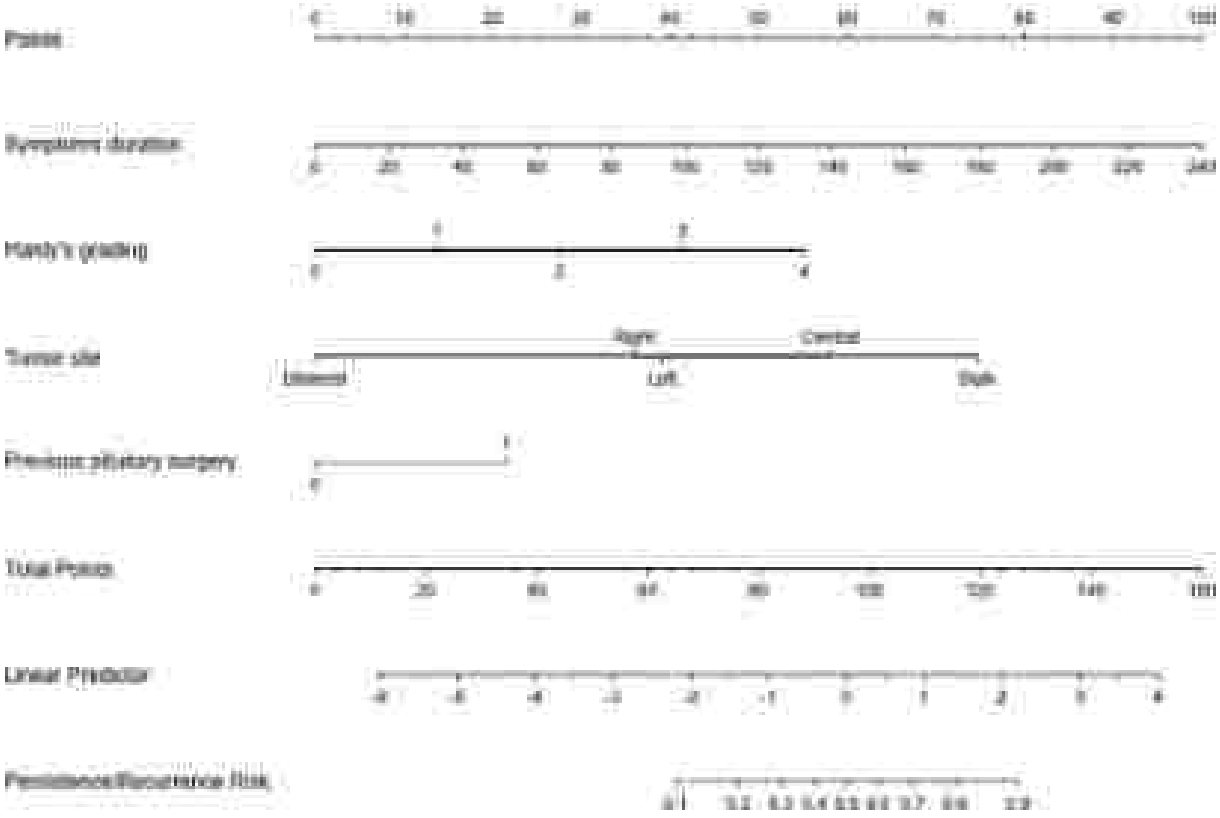

Fig. 5. Nomogram for predicting postoperative persistence or recurrence of Cushing's disease (PoRP-CD). This nomogram visually represents the predictive model for assessing the risk of recurrence or persistence of Cushing's disease following surgery. Each predictor variable—Symptom duration (months), Knosp grading, Hardy's grading, previous pituitary surgery, and tumor site—contributes a point value that aligns with the "Linear Predictor" axis, which maps to the "Probability of Persistence" axis, allowing estimation of recurrence likelihood.

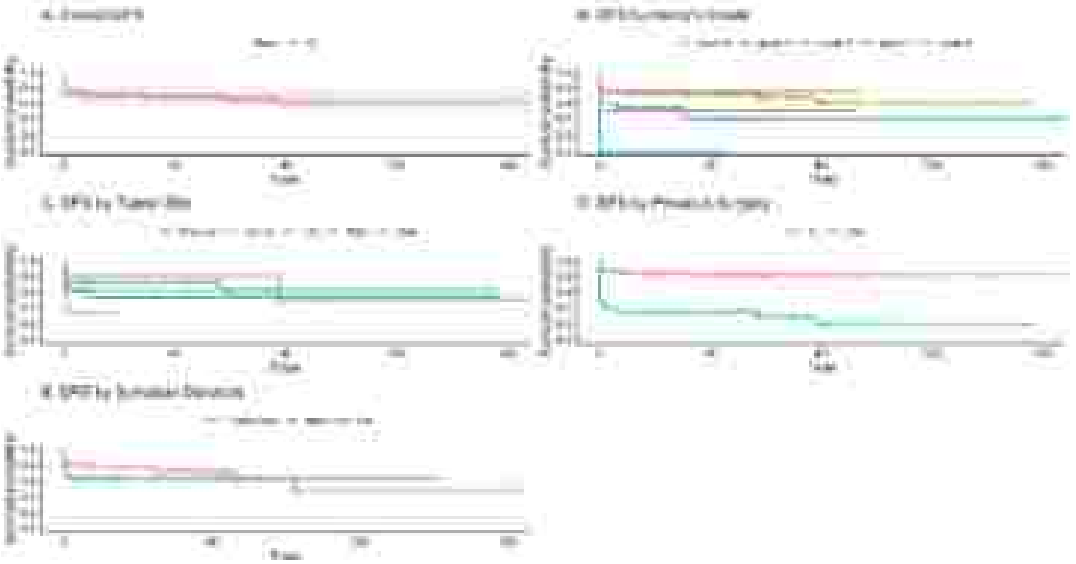

Fig. 6. Kaplan-Meier survival (DSS) analysis. (A) Kaplan-Meier curve of DSS for the entire cohort, showing a gradual decline over time; (B) DSS stratified by Hardy's Grade, demonstrating significant impact of grade on survival outcomes ($P < 0.05$); (C) DSS by tumor site, highlighting no significant association between tumor site and survival rate ($P = 0.06$); (D) DSS based on previous surgery status, indicating a higher risk of recurrence or death in patients with prior surgical interventions ($P < 0.01$); (E) DSS by symptom duration, highlighting no significant association ($P = 0.87$).

Furthermore, the development of an online dynamic nomogram bridges the gap between research and clinical practice, allowing personalized predictions and aiding surgeons in making informed decisions before pituitary surgery.

Although this study incorporated long-term follow-up (median 58 months), to define persistence and recurrence and to internally validate the model, external validation in prospective, multi-institutional cohorts remains essential to confirm its broader applicability. Although the CuPoR model incorporates a wide array of clinical, radiological, biochemical, and demographic variables, other potential prognostic

Table 3
Studies on predictive models of patients and tumour predictive factors of post-operative remission of Cushing's disease.

	Year	Country	Study Size	Methods	Main findings	Ref.
Predictive Models						
Comprising 8 factors: age, disease course, morning serum ACTH (preop), morning serum cortisol (preop), urine free cortisol (preop), morning serum ACTH ratio (postop), morning serum cortisol ratio (postop), urine free cortisol ratio (postop)	2019	China	354	Machine learning using Random Forest algorithm	Sensitivity 87 %, specificity 38 % AUC 0.78	[illegible]
Comprising 5 factors: age, disease course, morning serum ACTH (preop), morning serum cortisol ratio (postop), urine free cortisol ratio (postop)	2021	China	354	Deep learning using [illegible]-based neural approach	AUC 0.88	[illegible]
Predictive Factors						
Serum cortisol < 28 nmol/L (8–12 h after surgery)	1996	UK	11	Prospective	Favorable long-term remission rate	[illegible]
Serum 11-deoxycortisol > 150 nmol/L after metyrapone test at 14 days post-surgery	1997	Netherlands	25	Retrospective	Higher risk of recurrence Sensitivity 100 %, specificity 73 %	[illegible]
Serum cortisol < 5 μg/dL (3–8 d after surgery)	2001	Japan	46	Retrospective	Recurrent disease in 4 % of patients	[illegible]
MRI-based tumor size and cavernous sinus invasion	2008	Italy	38	Retrospective	Unfavorable factors of persistent disease	[illegible]
No histological evidence of adenoma	2007	US	460	Retrospective	Lower remission rate	[illegible]
Long-term hypocortisolism after surgery (>18 m)	2017	India	230	Retrospective	Favorable for remission Sensitivity 48 %, specificity 100 %	[illegible]
Greater decrease in BMI after surgery Lower DHEAS before surgery	2017	Taiwan	41	Retrospective	Favorable factors for higher remission	[illegible]
High serum ACTH/cortisol ratio before surgery	2018	Turkey	119	Retrospective	Risk factor for disease recurrence	[illegible]
USP8 mutation	2018	Germany	48	Retrospective	Higher remission rate	[illegible]
Serum cortisol < 107 nmol/L after dexamethasone suppression test following surgery	2018	Brazil	28	Interventional	Sensitivity 88 %, specificity 34 % AUC 0.62	[illegible]
Tumor visualization on MRI before surgery	2022	Spain	40	Retrospective	Favorable factor for remission	[illegible]

Abbreviations: ACTH – Adrenocorticotropic Hormone; AUC – Area Under the Curve; BMI – Body Mass Index; DHEAS – Dehydroepiandrosterone Sulfate; MRI – Magnetic Resonance Imaging; P-RR-CD – Persistent or Recurrent Cushing's Disease; Preop – Preoperative; Postop – Postoperative; USP8 – Ubiquitin Specific Peptidase 8.

factors were not included and may warrant consideration in future studies. For instance, the presence of meningoceles, degree of tumor invasion, and early recovery of the adrenal axis during the postoperative period have all been reported as relevant predictors of outcomes in Cushing's disease [26]. Moreover, the role of surgical expertise is critical, as higher surgeon and institutional experience are strongly associated with improved remission and lower recurrence rates [27]. Incorporating novel parameters, such as genetic markers or advanced imaging techniques, could further enhance the predictive accuracy and clinical utility of the model. Prospective implementation of the nomogram in routine clinical workflows will provide valuable insights into its performance and its potential to improve patient outcomes.

Conclusions

This study introduced a practical, predictive model for estimating the risk of postoperative persistence and recurrence in Cushing's disease, possibly offering a reliable tool for preoperative planning. By integrating key clinical predictors into an interactive online dynamic nomogram, the CuPeR model may provide surgeons with personalized risk assessments to aid in preoperative planning. Its focus on preoperative data ensures broader applicability, paving the way for tailored therapeutic strategies and improved patient outcomes in diverse clinical scenarios.

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CRediT authorship contribution statement

Guive Sharifi: Supervision, Conceptualization. Elham Paraandavaji: Investigation, Data curation. Nader Akbari Dilmaghani: Investigation, Data curation. Tohid Emami Meybodi: Investigation, Data curation. Ibrahim Mohammadzadeh: Investigation, Data curation. Negin alsadat Sadeghi: Investigation, Data curation. Amirali Vaghari: Visualization. Behnaz Nikoomandi: Visualization. Seyed Mohammad Tavangar: Resources. Mohammad reza Mohajeri Tehrani: Validation. Zahra Davoodi: Resources. Marjan Mirsalehi: Writing – review & editing. Seyed Ali Mousavinejad: Validation, Resources. Farzad Taghizadeh-Hesary: Writing – review & editing, Writing – original draft.

Informed consent

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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