

Long-Term Outcomes of Transsphenoidal Surgery for Pediatric Cushing's Disease: A Single-center Cohort With 313 Patient-years of Follow-up

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Research Article

Keywords: Cushing's disease, transsphenoidal surgery, corticotroph adenoma, long-term outcome

Posted Date: August 25th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10332982/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Pediatric Cushing's disease (CD) is rare, and long-term data on remission durability, morbidity reversal and reoperation outcomes after transsphenoidal surgery (TSS), especially from South Asia, are scarce. We report a single-center surgical cohort spanning 313 patient-years.

Methods

We retrospectively studied 37 consecutive children (≤ 18 years) who underwent TSS for CD at a tertiary neurosurgical center, with a salvage subset of nine children analyzed separately: seven underwent repeat transsphenoidal surgery and two bilateral adrenalectomy for disease. Pre- and post-operative biochemistry was compared using the Wilcoxon signed-rank test, and recurrence was expressed per person-time with Poisson confidence intervals.

Results

The median age at diagnosis was 14 years, and 54% of the patients were girls. Weight gain (86.5%) and hypertension (40.5%) were the most common features. Microadenomas predominated (83.8%; median 6 mm), and gross-total excision was achieved in 94.6%. Initial remission after surgery was achieved in 31 of 37 children (83.8%); after salvage treatment, the final remission rate was 36 of 37 (97.3%). Serum cortisol fell from 28.6 to 8.5 $\mu\text{g/dL}$ and ACTH from 60.3 to 24.2 pg/mL (both $p < 0.001$). Over a median follow-up of 130 months (total 313 patient-years), the recurrence/progression rate was 0.96 per 100 patient-years. Hypertension, diabetes, and obesity resolved in 75–85% of patients, menstrual cycles normalized in two-thirds, and salvage achieved remission in eight of nine.

Conclusions

TSS achieves durable remission with low morbidity in pediatric CD patients. Reoperation with or without radiotherapy salvages most children with persistent or recurrent disease; therefore, structured lifelong surveillance is warranted.

INTRODUCTION

Cushing's disease (CD), caused by chronic hypercortisolism resulting from an adrenocorticotrophic hormone (ACTH)-secreting corticotroph pituitary adenoma, is the most common cause of endogenous Cushing's syndrome beyond infancy but remains rare in childhood, with an incidence of approximately 5–10% of that in adults [1,2].

Pediatric CD has distinct clinical characteristics, most notably weight gain with impaired linear growth, which distinguishes it from simple childhood obesity. Other manifestations include virilization, pubertal delay,

menstrual disturbances, neuropsychiatric symptoms, hypertension, glucose intolerance, impaired bone mineralization, and reduced adult height if left untreated [1,3]. Unlike adults, pediatric CD demonstrates a more balanced sex distribution, with relative male predominance in younger children, and most tumors are small corticotroph microadenomas that are frequently difficult to localize on magnetic resonance imaging (MRI) (3–5).

Diagnosis requires biochemical confirmation of hypercortisolism and ACTH dependence, followed by pituitary localization using MRI and, when imaging is inconclusive, bilateral inferior petrosal sinus sampling [4,6].

Transsphenoidal surgery (TSS) remains the treatment of choice, achieving remission in 70–100% of children when performed in experienced multidisciplinary centers [2,6–8]. Persistent or recurrent disease may require repeat surgery, pituitary irradiation, bilateral adrenalectomy, or selected medical therapy (2, 6).

Despite several large pediatric surgical series from Europe, North America, and China, long-term outcome data from South Asia remain scarce, particularly regarding durable remission, endocrine and metabolic recovery, salvage surgery, and late recurrence [3,9]. Therefore, we evaluated the long-term outcomes of pediatric CD following TSS in a tertiary Indian neurosurgical center over 313 patient-years of follow-up.

METHODS

Study design and participants

We performed a retrospective cohort study at a tertiary academic referral centre where pediatric pituitary surgery is performed by a dedicated multidisciplinary team. Consecutive children (≤ 18 years) with biochemically confirmed ACTH-dependent Cushing's disease (CD), supported by histopathology where available, were identified from operative and endocrine records, and their medical records were reviewed. The study cohort comprised 37 children with CD who underwent transsphenoidal surgery. Salvage outcomes were analyzed separately in nine children, including seven who underwent repeat TSS and two who underwent bilateral adrenalectomy for persistent or recurrent disease. Children with adrenal, ectopic, or exogenous Cushing syndrome were excluded. Follow-up was censored at the most recent clinical visit.

Data collection

Data were extracted using a standardized proforma and included demographic, clinical, biochemical, radiological, operative, histopathological, and follow-up variables. The clinical data comprised presenting features, anthropometry, endocrine comorbidities, and bone mineral density, where available. Radiological assessment included pituitary MRI findings (lesion visibility, size, and invasiveness), and inferior petrosal sinus sampling was performed selectively for equivocal or discordant imaging. Operative variables included the surgical approach, extent of resection, blood loss, perioperative complications, and postoperative hormone replacement. Histopathological evaluation included ACTH and T-pit immunohistochemistry, granulation pattern, and Ki-67 index. Follow-up data included clinical, biochemical, radiological, and treatment outcomes.

Definitions and statistical analysis

CD was diagnosed according to the accepted criteria for ACTH-dependent pituitary hypercortisolism. Remission was defined by the final composite clinical, biochemical, and radiological status because postoperative cortisol sampling was not standardized across the cohort. Persistent disease was defined as failure to achieve sustained biochemical and clinical control after surgery; recurrence as disease re-emergence after documented remission; and partial response as incomplete or discordant control. Tumors ≤ 10 mm were classified as microadenomas, and cavernous sinus extension was graded using the Knosp–Steiner classification.

Continuous variables are presented as median (IQR) with range or frequency (%), as appropriate. Paired hormone concentrations were compared using the Wilcoxon signed-rank test, continuous associations using Spearman correlation, symptom clustering using tetrachoric correlation with hierarchical clustering, and recurrence as events per 100 patient-years with exact Poisson confidence intervals. Missing data were handled by complete-case analysis. Analyses were performed using R version 4.6.0, with two-sided $p < 0.05$ considered statistically significant. The study is reported according to the STROBE statement.

Ethics

The study was approved by the Institute Ethics Committee (approval no. AIIMSA1876/22.08.24) and conducted in accordance with the institutional guidelines for retrospective research, the International Council for Harmonization Good Clinical Practice (ICH–GCP), and the Indian Council of Medical Research (ICMR) guidelines. Patient identifiers were removed before analysis, and consent requirements were obtained in accordance with the approved protocol.

RESULTS

Cohort and follow-up (Table 1): Thirty-seven children underwent transsphenoidal surgery for Cushing disease. Follow-up was available for 36 (97%) children, with a median duration of 130 months (range, 1–180 months), providing 313 patient-years of observation for long-term outcome assessment.

Table 1. Baseline characteristics, clinical presentation, biochemistry, imaging and localisation (N=37).

Variable	Value
Demographics	
Sex — female / male	20 (54.1%) / 17 (45.9%)
Age at symptom onset, years	13 [11–15] (range 6–17.5)
Age at diagnosis, years	14 [12–17] (range 7–18)
Age at surgery, years	16 [13–17] (range 9–18)
Diagnostic delay, years	1 (range 0–3)
Presenting features, n (%)	
Weight gain	32 (86.5 %)
Truncal obesity	24 (64.9 %)
Skin striae	23 (62.2 %)
Hyperpigmentation	19 (51.4 %)
Hirsutism	16 (43.2 %)
Plethoric face	16 (43.2 %)
Proximal myopathy	15 (40.5 %)
Easy bruisability	14 (37.8 %)
Headache	14 (37.8 %)
Short stature / growth arrest	13 (35.1 %)
Fatigue	11 (29.7 %)
Acne	8 (21.6 %)
Psychiatric disturbance	4 (10.8 %)
Visual disturbance	3 (8.1 %)
Gynaecomastia	1 (2.7 %)
Galactorrhoea	1 (2.7 %)
Menstrual dysfunction (girls, n=19)	13 (68.4 %)
Comorbidities, n (%)	
Hypertension	15 (40.5 %)
Diabetes	5 (13.5 %)
Hypothyroidism	4 (10.8 %)
Anthropometry and bone	

Body mass index, kg/m²	24.9 [21.6–27.7] (15.6–39.0; n=23)
Osteoporosis / osteopenia (of n=10 assessed)	7 (70%) / 3 (30%)

Presentation and baseline characteristics of the study participants (Table 1). The cohort consisted predominantly of adolescents, with a median diagnostic delay of one year. Weight gain, truncal obesity, and skin striae were the predominant presenting features, whereas psychiatric and visual symptoms were rare. Hypertension was the most frequent endocrine comorbidity, and reduced bone mineral density was present in all children who underwent densitometry (Table 1).

Table 2. Key laboratory and imaging findings of the cohort (N=37).

Variable	Value
Biochemical findings (median [IQR])	
Pre-operative 0900 h Cortisol, µg/dL (RR 6.0–18.4)	27.5 [22.1–34.8] (n=37)
Pre-operative ACTH, pg/mL (RR 7.2–63)	61.1 [41.9–79.5] (n=34)
Imaging (3-Tesla MRI)	
Microadenoma / macroadenoma / MRI negative	31 (83.8%) / 3 (8.1%) / 3 (8.1%)
Discrete lesion visible	34 (91.9)
Maximum tumour dimension, mm	Median 6 (range 1–16; n=34)
MRI evidence of local invasion	3 (8.1 %)
Knosp grade 0 / 1 / 2 / 3 (of n=34)	27 / 4 / 1 / 2
Localisation – venous sampling	
Sampled	17/37 (45.9%)
Central (pituitary) source	13/17 (76.5%)
Lateralized / equivocal	3/1

Biochemistry, imaging, and localization (Table 2): Biochemical evaluation confirmed ACTH-dependent hypercortisolism in all children. MRI demonstrated a discrete pituitary lesion in most patients, predominantly microadenomas, whereas inferior petrosal sinus sampling confirmed a central pituitary source in most children undergoing evaluation. Radiological invasion was uncommon (Table 2 and supplementary Table S1).

Table 3. Operative details, peri-operative complications, histopathology and surgical outcome (N=37)

Variable	Value
<i>Surgical approach and extent</i>	
Endoscopic / microscopic	24 (64.9%) / 13 (35.1%)
Gross-total / near-total excision	35 (94.6%) / 2 (5.4%)
Estimated blood loss, mL	200 [100–300] (range 20–800)
<i>Peri-operative complications, n (%)</i>	
Intra-operative CSF leak	10/35 (28.6 %)
Post-operative CSF leak	1/36 (2.8 %)
Diabetes insipidus (transient)	10/37 (27.0 %)
Electrolyte imbalance	9/37 (24.3 %)
Visual deterioration / death	0 / 0
<i>Histopathology and proliferation</i>	
ACTH-immunopositive	19/20
T-pit positive	5/6
MIB-1/Ki-67 index, %	1.5 [1.0–4.5] (0.5–39; n=12)
Ki-67 > 3%	4/12 (33.3 %)
<i>Surgical outcome, n (%)</i>	
Initial remission	31/37 (83.8%)
Final remission	36/37 (97.3%)
Persistence	1/37 (2.7%)
Partial / mixed	0
<i>Paired biochemical change (Wilcoxon signed-rank)</i>	
Serum cortisol, µg/dL (n=35 pairs)	28.6 → 8.5; p=4.1×10 ⁻⁶
Plasma ACTH, pg/mL (n=26 pairs)	60.3 → 24.2; p=2.7×10 ⁻⁵

(Note: CSF, cerebrospinal fluid. Complication denominators vary (n=35–37) because operative records were incomplete for a small number of children; the paired biochemistry is restricted to children with both pre- and post-operative values, so its baseline medians differ slightly from the full-cohort medians in Table 1. The single tumour with a Ki-67 of 39% was a histologically confirmed, p53-negative aggressive corticotroph tumour).

Surgical and perioperative complications (Table 3): Gross-total resection was achieved in 94.6% of children. Intraoperative CSF leak, transient diabetes insipidus, and electrolyte imbalance were the most frequent

complications, whereas postoperative CSF leak was uncommon. No child experienced permanent visual deterioration or perioperative mortality (Table 3).

Histopathology (Table 3): Histopathology confirmed corticotroph differentiation in 19 of 20 evaluable tumours. Proliferative activity was generally low, although four tumours demonstrated Ki-67 indices >3%, including one aggressive corticotroph tumour with a Ki-67 index of 39% (Table 3).

Surgical outcomes and biochemical responses (Table 3 & Figure 1): Initial remission was achieved in 31 of 37 children (83.8%). Following salvage treatment for persistent or recurrent disease, the final remission rate increased to 97.3%. Paired analyses demonstrated significant postoperative reductions in serum cortisol and plasma ACTH concentrations (both $p < 0.001$; Figure 1).

Table 4. Long-term outcomes, endocrine recovery and recurrence

Variable	Value
Follow-up	
Duration, months (n=36)	130 [36–144] (range 1–180); mean 104
Total person-time	313.3 patient-years
Comorbidity resolution – improved / reassessed (%)	
Hypertension	9/11 (82 %)
Diabetes	3/4 (75 %)
Obesity	23/27 (85 %)
Menstrual status at last follow-up (girls, n=12 classifiable), n (%)	
Regular / resumed	8 (66.7 %)
Irregular / oligomenorrhoea	4 (33.3 %)
Persistent amenorrhoea	0 (0)
Serial serum cortisol trajectory, µg/dL (n=9)	
Pre-operative / post-operative / recent	22.3 / 3.3 / 7.4
Recurrence / progression	
Events	3
Rate per 100 patient-years (95% CI)	0.96 (0.20–2.80)
Salvage cohort (n=9) – summary	
Final remission / persistent	8/1
Adjuvant radiotherapy or gamma-knife; bilateral adrenalectomy	3/9; 2/9

Long-term outcomes and recurrence (Table 4): During follow-up, hypertension, diabetes, obesity, and menstrual dysfunction improved in most reassessed children. Three recurrences occurred during 313 patient-years of observation, corresponding to a recurrence rate of 0.96 per 100 patient-years. Serial serum cortisol measurements demonstrated sustained biochemical remission in most children.

Table 5. Salvage treatment and outcomes in children with persistent or recurrent Cushing's disease (n = 9).

ID	Disease status (interval)	Redo EETS	Adjuvant treatment	Final outcome
P1	Recurrence (at 8 mo)	Yes ×1	—	Remission
P2	Recurrence (at 32 mo)	Yes ×1	—	Remission
P3	Persistent	Yes ×1	Radiotherapy 50.4 Gy	Persistent
P4	Persistent	Yes ×1	Gamma-knife	Remission
P5	Persistent	Yes ×1	Gamma-knife	Remission
P6	Recurrence (at 24 mo)	Yes ×1	—	Remission
P7	Persistent	Yes ×2	—	Remission
P8	Persistent	No	Bilateral adrenalectomy	Remission
P9	Persistent	No	Bilateral adrenalectomy	Remission

Exploratory analyses and salvage treatment were performed (Table 5, Figure 2): Repeat transsphenoidal surgery was the commonest salvage strategy, with radiotherapy, gamma-knife radiosurgery, or bilateral adrenalectomy reserved for selected patients. Salvage treatment achieved remission in eight of nine children (Table 5). Exploratory symptom clustering identified distinct catabolic, metabolic, and androgenic phenotypes, with hyperpigmentation inversely associated with hirsutism (Figure 2; Supplementary Table S2).

Discussion

In this single-center series of 37 children with Cushing's disease, transsphenoidal surgery provided durable long-term disease control, achieving a final remission rate of 97.3% with low morbidity and no perioperative mortality. The prolonged follow-up of 313 patient-years demonstrated sustained biochemical remission, substantial recovery of hypercortisolism-related comorbidities, and successful salvage in most children with persistent or recurrent disease. Together, these findings reinforce the role of surgery as the primary treatment for pediatric Cushing's disease in experienced multidisciplinary centers.

The demographic and clinical profiles of our cohort were comparable to those of contemporary pediatric series. The near-equal sex distribution (54% girls) and median age at diagnosis of 14 years closely resemble the largest prospective multisite cohort (56% females; median age 13 years) [3], consistent with the disappearance of male predominance seen in younger children [1]. Weight gain remained the dominant

presenting feature (86.5%), as consistently reported in previous studies [1,3]. Hypertension (40.5%), dysglycemia (13.5%), and growth failure (35%) were less frequent than in predominantly prepubertal cohorts [3,10,11], likely reflecting the predominantly adolescent composition of our series. The median diagnostic delay of one year was shorter than the approximately two years reported in multicenter (3) and UK cohorts (10), although retrospective ascertainment of symptom onset may have contributed to this finding.

Our final remission rate of 97.3% lies at the upper end of the 70–100% reported for pediatric CD (1, 2) and approaches the 98% achieved in the National Institutes of Health (NIH) series (7). Comparable long-term outcomes have been reported in China (81.8%) (12), the United Kingdom (76%) (10), and the University of Virginia, where remission increased from 76% after primary surgery to 91% after salvage treatment (13). Lower rates have been observed in cohorts enriched with macroadenomas (5). Marked postoperative reductions in serum cortisol (28.6 to 8.5 µg/dL) and plasma ACTH (60.3 to 24.2 pg/mL) confirmed effective corticotroph ablation, while the low persistent disease rate (2.7%) likely reflected successful salvage treatment. Together with the prolonged follow-up, these findings further support the current recommendations favoring management in experienced multidisciplinary pituitary centers (4, 6).

Radiological–pathological discordance was one of the most notable findings. MRI identified a discrete lesion in 92% of children, whereas histological confirmation of adenoma was obtained in only 53%, with normal pituitary tissue identified in 47% of cases. Similar discrepancies have been recognized in previous pediatric series, where MRI detection ranges from 43% to 87%, despite higher histological confirmation rates (3, 9, 12, 14–16). Inferior petrosal sinus sampling confirmed a central pituitary source in 77% of the sampled children but showed limited lateralizing accuracy, consistent with previous reports [17,18]. The lack of correlation between cortisol concentration and tumor size further reflects the predominance of functioning microadenomas. Although proliferative activity was generally low, one-third of tumors demonstrated a Ki-67 index $\geq 3\%$, comparable with previous pediatric studies [14], while one tumor exhibited a Ki-67 index of 39%, indicating aggressive biological behavior [19,20]. These findings highlight that successful management requires integration of biochemical, radiological, and intraoperative assessments, as histologically normal tissue does not exclude remission [3,7,17].

The perioperative outcomes of our cohort further support the safety of transsphenoidal surgery for pediatric CD when performed in experienced multidisciplinary centers. Contemporary pooled analyses have reported an overall complication rate of approximately 23% (21). Transient diabetes insipidus (27.0%) and intra-operative cerebrospinal fluid (CSF) leak (28.6%) were the most frequent complications and exceeded pooled estimates of approximately 13% (21) and the benchmarked incidence of postoperative hyponatremia (13.3%) (22). However, only one child (2.8%) developed a persistent postoperative CSF leak, all cases of diabetes insipidus resolved, and there were no instances of visual deterioration or perioperative mortality. The relatively high intraoperative CSF leak rate likely reflects the extensive exploration required to localize small, frequently MRI-discordant corticotroph microadenomas. Overall, our findings are comparable with those of recent pediatric studies (10, 23) and reinforce the evidence that endoscopic and microscopic transsphenoidal surgeries have similar safety profiles when performed in specialized centers [10,21,24,25].

The extended follow-up period represents a major strength of this study, permitting a robust assessment of durable remission and recurrence. The extended follow-up of 130 months (313 patient-years) allowed

assessment of late recurrences and long-term endocrine recovery, outcomes that are often incompletely captured in shorter pediatric series. Our recurrence rate (0.96 per 100 patient-years) lies at the lower end of that reported in comparable pediatric cohorts [2,3,9,12,14]. The marked postoperative decline followed by gradual recovery of serum cortisol is consistent with the progressive restoration of hypothalamic–pituitary–adrenal axis function and supports the need for lifelong biochemical surveillance after apparent cure (9, 11). Hypercortisolism-related morbidity improved substantially, with hypertension, diabetes, obesity, menstrual dysfunction, and reduced bone mineral density showing favorable recovery, consistent with previous pediatric studies demonstrating the reversal of metabolic, cardiovascular, skeletal, and gonadal sequelae following biochemical remission (3, 9, 26, 27). To our knowledge, this represents one of the longest reported contemporary pediatric Cushing's disease surgical series from South Asia, with 313 patient-years of follow-up, providing clinically relevant data on durable remission, recurrence, and long-term endocrine recovery. Growth outcomes could not be evaluated because height standard deviation scores and growth velocity were unavailable, despite their importance in pediatric CD (1, 9, 11).

Previous studies have identified adenoma identification, ACTH immunopositivity, absence of invasion, and postoperative morning cortisol levels < 1 µg/dL as the strongest predictors of durable remission (7, 28). Consistent with comparative studies, we observed no meaningful advantage of endoscopic over microscopic surgery regarding remission, recurrence, or complications, apart from shorter hospitalization after endoscopic surgery (29). Although endoscopy provides superior illumination and a wider panoramic view, these advantages may be attenuated in pediatric patients because of a narrower nasal corridor, variable sphenoid sinus pneumatization, and smaller sellar anatomy, which can make surgical exposure and instrument manoeuvrability more challenging, particularly in younger children (24, 25). Consequently, when surgery is performed in experienced multidisciplinary pituitary centres, remission appears to depend more on accurate tumour localisation and surgical expertise than on the operative approach itself. The exploratory symptom co-occurrence analysis identified distinct catabolic–metabolic and androgenic phenotypes, with hyperpigmentation inversely associated with hirsutism, a finding that requires validation in larger cohorts [3]. Salvage treatment achieved remission in eight of nine children, supporting the established roles of repeat surgery, radiotherapy, stereotactic radiosurgery, and bilateral adrenalectomy for persistent or recurrent diseases [2,6,20,30]. Although invasive tumors were uncommon (8.1%), all patients achieved remission despite the recognized adverse prognostic impact of cavernous sinus invasion (13, 14).

The principal strengths of this study are its regional size, exceptionally long follow-up, comprehensive assessment of recovery outcomes, and conservative statistical approach without data imputation. Limitations include the retrospective single-center design, limited outcome events, incomplete endocrine and molecular data, absence of detailed growth assessment and complete clinicopathological grading, reliance on a composite remission definition, and predominance of adolescent patients. Because the study spanned a prolonged recruitment period, immediate postoperative cortisol sampling was not standardized throughout the cohort; consequently, remission was defined using a composite clinical, biochemical, and radiological assessment rather than a uniform early postoperative cortisol threshold. Prospective multicenter studies with standardized endocrine assessments and outcome measures are required to validate these findings.

Conclusion

Transsphenoidal surgery provides durable long-term remission with low morbidity in pediatric Cushing's disease when performed in experienced multidisciplinary pituitary centres. Although localization of small corticotroph adenomas remains challenging because of frequent radiological–histopathological discordance, excellent long-term disease control is achievable, and repeat surgery with selective adjuvant therapy effectively salvages most children with persistent or recurrent disease. Our findings reinforce the importance of referral to specialised pituitary centres and lifelong clinical, biochemical, and radiological surveillance to optimise long-term outcomes.

Declarations

Declaration of interest

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

Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author Contribution

All authors contributed to the conception and design of the study. Material preparation, data collection, and data analysis were performed by B.M. and A.K. . Statistical analysis was performed by B.M. and A.K. Data required was provided by V.S. , R.K., N.T. , S.B.,A.S., , The first draft of the manuscript was written by B.M. and A.K., and all authors critically reviewed, revised, and approved the final manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Acknowledgement

We would like to thank the residents, nursing officers , and hospital staff involved in the overall treatment of the patients and Dr. Chandra Kiran A for coordinating the electronic submission of the manuscript

Data Availability

The data that support the findings of this study are available in the concerned departments in AIIMS NEW DELHI, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. The data are, however, available upon request and with the permission of concerned departments in AIIMS NEW DELHI.

References

1. Ferrigno R, Hasenmajer V, Caiulo S, Minnetti M, Mazzotta P, Storr HL et al (2021) Paediatric Cushing's disease: Epidemiology, pathogenesis, clinical management and outcome. *Rev Endocr Metab Disord* 22(4):817–835. 10.1007/s11154-021-09626-4 PubMed PMID: 33515368; PubMed Central PMCID: PMC8724222
2. Savage MO, Ferrigno R (2024) Paediatric Cushing's disease: long-term outcome and predictors of recurrence. *Front Endocrinol (Lausanne)* 15:1345174. 10.3389/fendo.2024.1345174 PubMed PMID: 38318299; PubMed Central PMCID: PMC10838966
3. Tatsi C, Kamilaris C, Keil M, Saidkhodjaeva L, Faucz FR, Chittiboina P et al (2024) Paediatric Cushing syndrome: a prospective, multisite, observational cohort study. *Lancet Child Adolesc Health* 8(1):51–62. 10.1016/S2352-4642(23)00264-X PubMed PMID: 38097317; PubMed Central PMCID: PMC11245730
4. Korbonits M, Blair JC, Boguslawska A, Ayuk J, Davies JH, Druce MR et al (2024) Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 2, specific diseases. *Nat Rev Endocrinol* 20(5):290–309. 10.1038/s41574-023-00949-7 PubMed PMID: 38336898
5. Yami Channaiah C, Memon SS, Sarathi V, Lila AR, Sankhe S, Arya S et al (2024) Pediatric Macrocorticotropinoma: Do They Differ from Microcorticotropinoma? *Neuroendocrinology* 114(1):42–50 doi:10.1159/000533770 PubMed PMID: 37634509
6. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR et al (2021) Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol* 9(12):847–875. 10.1016/S2213-8587(21)00235-7 PubMed PMID: 34687601; PubMed Central PMCID: PMC8743006
7. Lonser RR, Wind JJ, Nieman LK, Weil RJ, DeVroom HL, Oldfield EH (2013) Outcome of surgical treatment of 200 children with Cushing's disease. *J Clin Endocrinol Metab* 98(3):892–901. 10.1210/jc.2012-3604 PubMed PMID: 23372173; PubMed Central PMCID: PMC3590477
8. Chandler WF, Barkan AL, Hollon T, Sakharova A, Sack J, Brahma B et al (2016) Outcome of Transsphenoidal Surgery for Cushing Disease: A Single-Center Experience Over 32 Years. *Neurosurgery* 78(2):216–223. 10.1227/NEU.0000000000001011 PubMed PMID: 26348007
9. Yordanova G, Martin L, Afshar F, Sabin I, Alusi G, Plowman NP et al (2016) Long-term outcomes of children treated for Cushing's disease: a single center experience. *Pituitary* 19(6):612–624. 10.1007/s11102-016-0756-8 PubMed PMID: 27678103; PubMed Central PMCID: PMC5080319
10. Elnaggar AM, Dattani M, Gan HW, Storr HL, Matthew Matson null, Drake WM et al (2025) Cushing's disease in children: a single-centre experience. *Childs Nerv Syst* ;41(1):293. 10.1007/s00381-025-06952-9 PubMed PMID: 40996550
11. Davies JH, Storr HL, Davies K, Monson JP, Besser GM, Afshar F et al (2005) Final adult height and body mass index after cure of paediatric Cushing's disease. *Clin Endocrinol (Oxf)* 62(4):466–472.

- 10.1111/j.1365-2265.2005.02244.x PubMed PMID: 15807878
12. Wang B, Zhang H, Su T, Ren J, Sun Q, Sun Y et al (2025) The neurosurgical outcome of pediatric Cushing's disease in a single center from China: a 20-year experience. *Front Endocrinol (Lausanne)* 16:1663624. 10.3389/fendo.2025.1663624 PubMed PMID: 40969365; PubMed Central PMCID: PMC12440734
 13. Kanter AS, Diallo AO, Jane JA, Sheehan JP, Asthagiri AR, Oskouian RJ et al (2005) Single-center experience with pediatric Cushing's disease. *J Neurosurg* 103(5 Suppl):413–420. 10.3171/ped.2005.103.5.0413 PubMed PMID: 16302612
 14. Zheng X, Wang H, Zhang W, Feng S, Liu Y, Li S et al (2021) Diagnosis, Manifestations, Laboratory Investigations, and Prognosis in Pediatric and Adult Cushing's Disease in a Large Center in China. *Front Endocrinol (Lausanne)* 12:749246. 10.3389/fendo.2021.749246 PubMed PMID: 34867792; PubMed Central PMCID: PMC8640923
 15. Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB et al (1994) Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N Engl J Med* 331(10):629–636. 10.1056/NEJM199409083311002 PubMed PMID: 8052272
 16. Batista D, Courkoutsakis NA, Oldfield EH, Griffin KJ, Keil M, Patronas NJ et al (2005) Detection of adrenocorticotropin-secreting pituitary adenomas by magnetic resonance imaging in children and adolescents with cushing disease. *J Clin Endocrinol Metab* 90(9):5134–5140. 10.1210/jc.2004-1778 PubMed PMID: 15941871
 17. Kang KM, Muralidharan K, Knowlton H, Hassan KIA, Yekula A, Misra M et al (2022) Utility of bilateral inferior petrosal sinus sampling for diagnosis and lateralization of Cushing's disease in the pediatric population: case series and review of the literature. *J Endocrinol Invest* 45(3):617–627. 10.1007/s40618-021-01680-8 PubMed PMID: 34655038
 18. Virú-Loza MA, Quispe AV (2022) Diagnostic Power of Bilateral Inferior Petrosal Sinus Sampling with Desmopressin in Paediatric Cushing's Disease. *J Clin Res Pediatr Endocrinol* 14(3):334–338. 10.4274/jcrpe.galenos.20222022-12-9 PubMed PMID: 35308013; PubMed Central PMCID: PMC9422914
 19. Sahakian N, Goetz L, Appay R, Graillon T, Raingeard I, Piazzola C et al (2024) Outcome of non-functioning ACTH pituitary tumors: silent does not mean indolent. *Pituitary* 27(5):644–653. 10.1007/s11102-024-01428-6 PubMed PMID: 38995473
 20. Kara M, Güdük M, Samanci Y, Yilmaz M, Şengöz M, Peker S (2020) Gamma knife radiosurgery in patients with Cushing's disease: Comparison of aggressive pituitary corticotroph tumor versus corticotroph adenoma. *Clin Neurol Neurosurg* 197:106151. 10.1016/j.clineuro.2020.106151 PubMed PMID: 32882541
 21. Stefanidis P, Kyriakopoulos G, Athanasouli F, Mytareli C, Tzanis G, Korfias S et al (2022) Postoperative complications after endoscope-assisted transsphenoidal surgery for pituitary adenomas: a case series, systematic review, and meta-analysis of the literature. *Horm (Athens)* 21(3):487–499. 10.1007/s42000-022-00362-1 PubMed PMID: 35277844
 22. Webb KL, Reilly CE, Hinkle ML, Shinya Y, Van Gompel JJ, Meyer FB (2025) Incidence and risk factors of hyponatremia after transsphenoidal surgery: a systematic meta-analysis. *Neurosurg Rev* 48(1):630. 10.1007/s10143-025-03784-8 PubMed PMID: 40892282
 23. Sharifi G, Paraandavaji E, Nasab MMM, Mohammadi E, Sadeghi N, Tavangar SM et al (2025) Clinical and surgical outcomes of pediatric Cushing's disease following endoscopic transsphenoidal surgery. *Childs*

Nerv Syst 41(1):130. 10.1007/s00381-025-06790-9 PubMed PMID: 40090938

24. Locatelli D, Veiceschi P, Castelnovo P, Tanriover N, Evliyaoglu O, Canaz H et al (2019) Transsphenoidal surgery for pituitary adenomas in pediatric patients: a multicentric retrospective study. *Childs Nerv Syst* 35(11):2119–2126. 10.1007/s00381-019-04179-z PubMed PMID: 31079182
25. Marino AC, Taylor DG, Desai B, Jane JA (2019) Surgery for Pediatric Pituitary Adenomas. *Neurosurg Clin N Am* 30(4):465–471. 10.1016/j.nec.2019.05.008 PubMed PMID: 31471053
26. Lodish MB, Sinaii N, Patronas N, Batista DL, Keil M, Samuel J et al (2009) Blood pressure in pediatric patients with Cushing syndrome. *J Clin Endocrinol Metab* 94(6):2002–2008. 10.1210/jc.2008-2694 PubMed PMID: 19293264; PubMed Central PMCID: PMC2690429
27. Wagenmakers Ma, Roerink EM, Schreuder SHPP, Plantinga THA, Holewijn TS, Thijssen S (2016) Vascular Health in Patients in Remission of Cushing's Syndrome Is Comparable With That in BMI-Matched Controls. *J Clin Endocrinol Metab* 101(11):4142–4150. 10.1210/jc.2016-1674 PubMed PMID: 27552540
28. Albani A, Theodoropoulou M (2021) Persistent Cushing's Disease after Transsphenoidal Surgery: Challenges and Solutions. *Exp Clin Endocrinol Diabetes* 129(3):208–215. 10.1055/a-1220-6056 PubMed PMID: 32838436
29. Trimpou P, Backlund E, Ragnarsson O, Skoglund T, Hallén T, Gudnadottir G et al (2022) Long-Term Outcomes and Complications from Endoscopic Versus Microscopic Transsphenoidal Surgery for Cushing's Disease: A 15-Year Single-Center Study. *World Neurosurg* 166:e427–e434. 10.1016/j.wneu.2022.07.027 PubMed PMID: 35840092
30. Gheorghiu ML, Fleseriu M, STEREOTACTIC RADIATION THERAPY IN PITUITARY ADENOMAS, IS IT BETTER THAN CONVENTIONAL RADIATION THERAPY? (2017) *Acta Endocrinol (Buchar)* 13(4):476–490. 10.4183/aeb.2017.476 PubMed PMID: 31149219; PubMed Central PMCID: PMC6516550

Figures

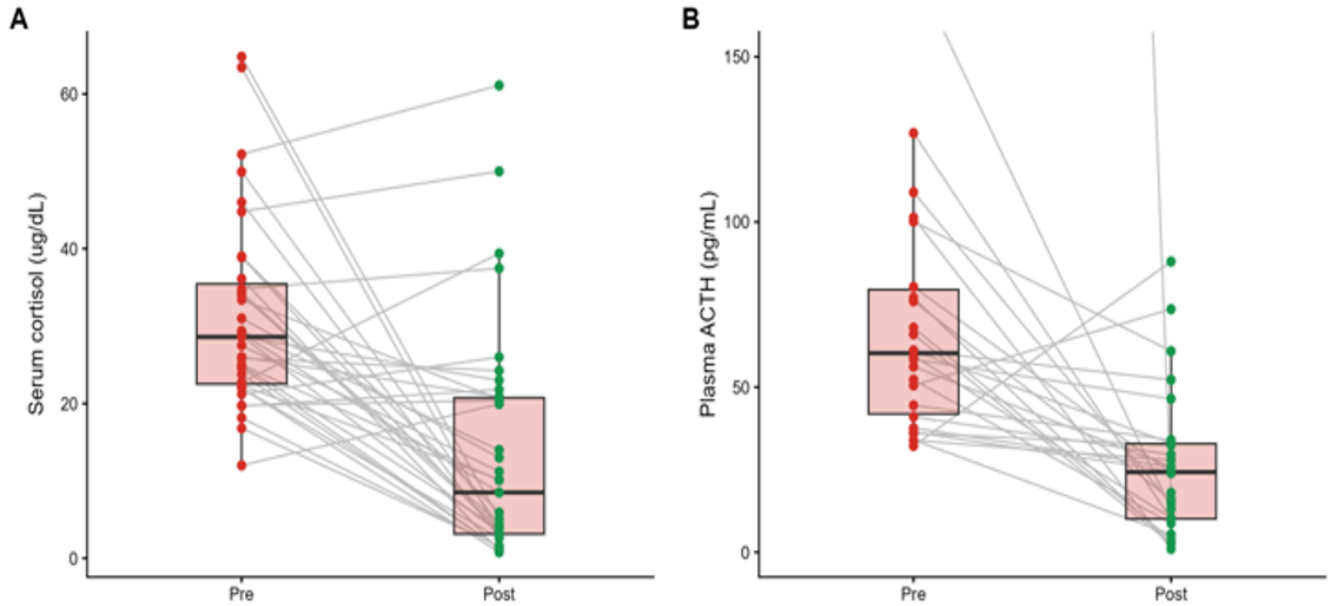


Figure 1

Paired biochemical response following transsphenoidal surgery for pediatric Cushing disease. (A) Paired pre- and postoperative serum cortisol concentrations. (B) Paired preoperative and postoperative plasma ACTH concentrations. In panels A and B, individual patients are connected by gray lines, and boxplots represent the median and interquartile range. The ACTH axis in panel B was truncated at 150 pg/mL for clarity.

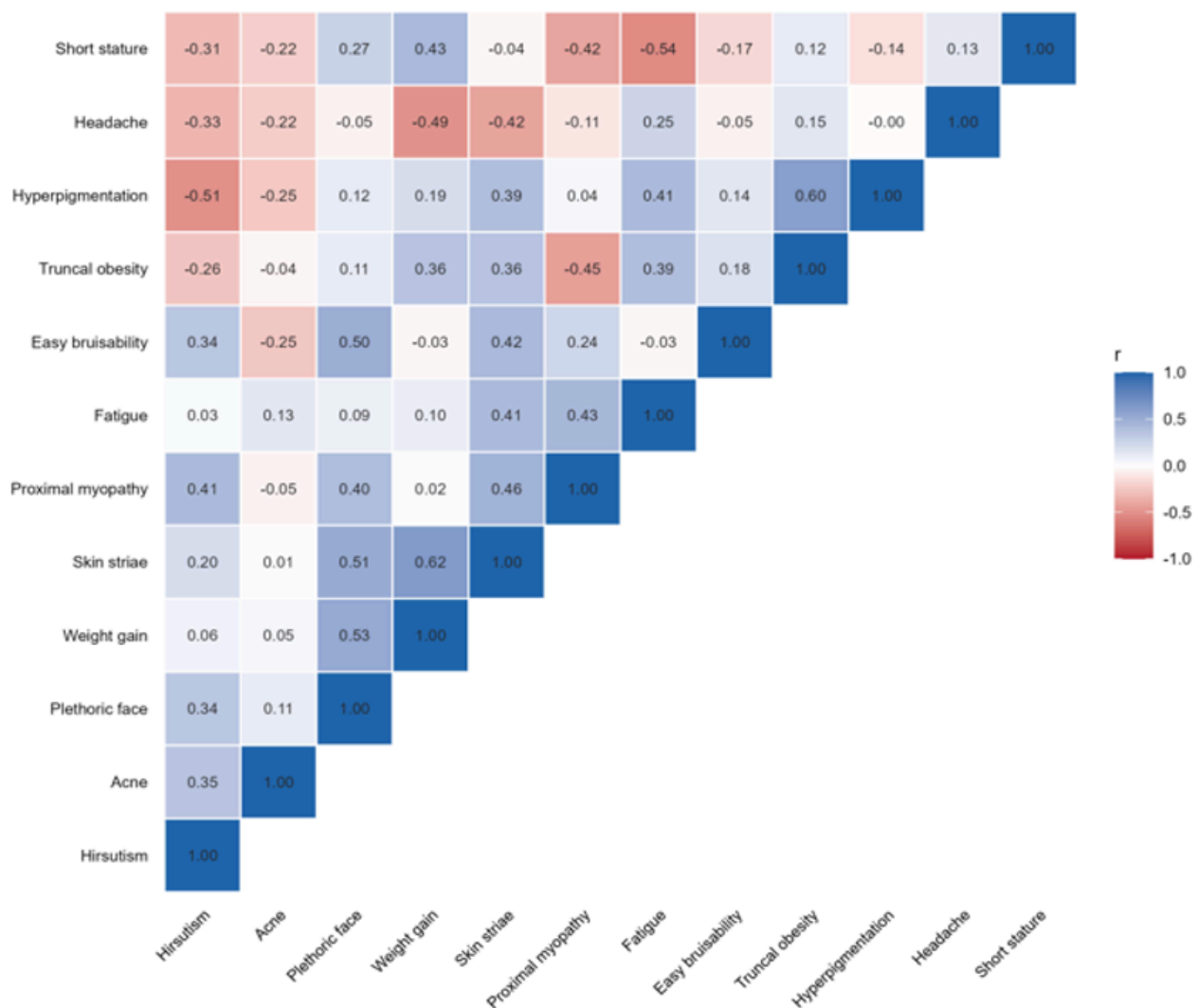


Figure 2

Exploratory symptom correlation heatmap in pediatric Cushing's disease. Pairwise tetrachoric correlation coefficients with hierarchical clustering demonstrated co-occurrence patterns among the presenting clinical features. Positive correlations are shown in blue and negative correlations are shown in red. Distinct catabolic-metabolic and androgenic symptom clusters were identified, with an inverse association between hyperpigmentation and hirsutism. This exploratory analysis was hypothesis-generating and requires validation in larger cohorts.

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