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Perioperative clinical and pathological features and postoperative endocrine complications of apoplectic versus non- apoplectic pituitary adenomas: a comparative study based on intraoperative intrasellar pressure stratification

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Abstract

Purpose

Using a standardized three-tier intraoperative intrasellar pressure (ISP) stratification, we compared the perioperative clinical, imaging, and pathological features of pituitary adenomas with and without apoplexy, identified independent risk factors for apoplexy and postoperative complications, and evaluated the screening performance of ISP.

Methods

This single-center retrospective cohort included 217 patients with primary pituitary neuroendocrine tumors (Pit-NETs, also known as pituitary adenomas) undergoing endoscopic transsphenoidal surgery (January 2023–May 2026), classified into apoplexy (n = 46) and non-apoplexy (n = 171) groups, and into low (< 15 mmHg, n = 42), intermediate (15–24 mmHg, n = 109), and high (≥ 25 mmHg, n = 66) ISP tiers. Variables significant in univariate analyses ($P < 0.05$) entered two binary multivariable logistic regression models; predictive performance was assessed by receiver operating characteristic (ROC) analysis.

Results

Apoplexy was associated with larger tumors, hyperprolactinemia, nonfunctioning adenomas, multi-axis hypopituitarism, severe headache, visual deficits, greater blood loss, longer operative time, higher ISP, intratumoral hemorrhage/necrosis, tumor invasiveness, and higher Ki-67 indices (all $P < 0.05$). Hypertension, hyperprolactinemia, and ISP ≥ 25 mmHg independently predicted apoplexy (area under the curve [AUC] = 0.889 for ISP ≥ 25 mmHg). Apoplexy, tumor invasiveness, Ki-67 ≥ 3%, maximal tumor diameter ≥ 3 cm, blood loss ≥ 300 mL, and ISP ≥ 25 mmHg independently predicted postoperative complications.

Conclusion

Elevated intraoperative ISP is a core independent risk factor for pituitary apoplexy and postoperative endocrine and diaphragm-related complications. Routine standardized ISP monitoring with tiered risk management is recommended.

Introduction

Pituitary neuroendocrine tumors (Pit-NETs, also known as pituitary adenomas) are the most common endocrine tumors of the sellar region, and approximately 2–16% of patients develop pituitary apoplexy during the disease course [1–4]. Apoplexy, characterized pathologically by spontaneous intratumoral hemorrhage and coagulative necrosis, mechanically compresses the anterior pituitary lobe, the pituitary

stalk, and the optic nerves, rapidly precipitating panhypopituitarism, intractable headache, and visual impairment; severe cases may present with disturbed consciousness [4]. Even after emergency surgery, permanent diabetes insipidus and persistent hypopituitarism remain far more frequent in patients with apoplexy than in those with non-apoplectic Pit-NETs, necessitating long-term hormone replacement therapy and seriously compromising endocrine homeostasis and quality of life [20].

Current preoperative risk stratification for Pit-NETs relies solely on morphological imaging indicators such as tumor size and the Knosp cavernous sinus grade, which reflect mass effect only indirectly, and an objective, intraoperatively quantifiable indicator of the mechanical compression load on the pituitary gland is lacking [5–7]. Intrasellar pressure (ISP) directly quantifies the sustained compression exerted by the tumor on the pituitary portal system and normal endocrine cells. Previous basic research has confirmed that elevated ISP causes pituitary microcirculatory stasis and chronic tissue hypoxia, activates the hypoxia-inducible factor-1α (HIF-1α) pathway, upregulates aberrant vascular endothelial growth factor-driven angiogenic signaling, and aggravates prolactin dysregulation, forming a vicious cycle of "high pressure–hypoxia–hormonal disturbance–intratumoral hemorrhage" [8]. Small-sample clinical observations have suggested a higher incidence of pituitary apoplexy in high-ISP populations [9]; however, existing cohorts are predominantly Western, have used only binary pressure classification, and no ISP-based endocrine risk prediction model is available. Studies of risk factors for pituitary apoplexy have likewise focused on systemic and morphological indicators such as hypertension and giant tumors, without incorporating local intrasellar mechanical compression—the core variable that directly injures endocrine tissue [10, 11].

Standardized quantitative intraoperative ISP measurement using the Codman microsensor has become the internationally recognized gold standard, and the endoscopic transsphenoidal approach permits standardized ISP measurement under direct visualization [12, 13]. Notably, our group's previous analysis of 84 patients reported no significant correlation between ISP and pituitary apoplexy; however, that conclusion was constrained by the limited sample size and an insufficient number of apoplexy events, and required validation or revision in a larger cohort [14]. The quantitative relationship between the ISP gradient and postoperative endocrine outcomes also remains unexplored.

To address these gaps, the present study drew on a consecutive cohort of 217 patients to systematically evaluate the value of a three-tier ISP stratification scheme for predicting pituitary apoplexy, invasive tumor phenotypes, and postoperative endocrine complications, aiming to establish a risk stratification system integrating intrasellar mechanical load, hormone levels, and pathological proliferation indices, and to provide an evidence base for individualized perioperative endocrine management of Pit-NETs.

Materials and methods

Study design and ethics approval

This was a single-center, consecutive retrospective cohort study, reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The protocol was approved by the Ethics Committee of Bengbu Medical University (approval No. 2022KY064). All clinical data were de-identified, and the study was conducted in strict accordance with the Declaration of Helsinki. Given the retrospective nature of the archived data, the ethics committee waived the requirement for written informed consent.

Study population

A total of 217 patients with primary sellar neuroendocrine tumors who underwent endoscopic endonasal transsphenoidal tumor resection in the Department of Neurosurgery, The First Affiliated Hospital of Bengbu Medical University, between January 2023 and May 2026 were enrolled.

The inclusion criteria were: (1) postoperative pathological confirmation of a Pit-NET; (2) a complete preoperative pituitary hormone panel and contrast-enhanced sellar magnetic resonance imaging (MRI), completion of standardized intraoperative ISP measurement, and complete baseline data; (3) absence of other intracranial tumors, cerebrovascular malformations, and severe functional failure of vital organs; and (4) complete follow-up of at least 3 months without missing pituitary function re-examination data.

The exclusion criteria were: (1) concomitant systemic malignancy or uncontrolled active infection; (2) preoperative radiotherapy, chemotherapy, or long-term hormone intervention; (3) recurrent or metastatic pituitary tumors; and (4) missing key endocrine, pathological, or follow-up data.

Grouping criteria

Apoplexy versus non-apoplexy grouping. A triple diagnostic standard combining pathology, imaging, and clinical presentation was applied. Pathologically confirmed intratumoral hemorrhage or necrosis was a mandatory condition; patients additionally presenting with mixed hemorrhagic signals within the tumor on preoperative MRI or with typical symptoms of acute pituitary failure were assigned to the apoplexy group (n = 46); the remaining 171 patients constituted the non-apoplexy group.

ISP stratification. The three-tier cutoffs (15 and 25 mmHg) were derived from large-scale international intraoperative measurement studies and adopted by the recent endoscopic cohorts of the Simander group [12, 13]: G1 (low, ISP < 15 mmHg, n = 42), below the physiological upper limit of normal intrasellar pressure [15, 16]; G2 (intermediate, 15–24 mmHg, n = 109); and G3 (high, ≥ 25 mmHg, n = 66), the critical threshold for high-risk acute hemorrhage identified by Zayour et al. [17].

Preoperative evaluation and standardized ISP measurement

All patients underwent preoperative complete blood count, coagulation function, liver and kidney function, serum electrolytes, and a full pituitary hormone panel (prolactin, growth hormone,

adrenocorticotropic hormone, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone). Plain head computed tomography and contrast-enhanced sellar MRI were performed to quantify the maximal tumor diameter, tumor volume, suprasellar extension, cavernous sinus invasion (Knosp grade), and diaphragmatic morphology. Intraoperative ISP was measured under direct endoscopic visualization using a Codman® MicroSensor intracranial pressure probe (Integra LifeSciences, Mansfield, MA, USA), strictly following the standardized protocols established by Simander et al. [12, 13]: before tumor resection, a 2-mm micro-fenestration was drilled in the sellar floor and a 1.5-mm sharp dural incision was made to avoid substantial cerebrospinal fluid (CSF) leakage; after calibration, the sensor was advanced approximately 5 mm into the sellar cavity and allowed to equilibrate for 30 s until the pressure waveform stabilized; ISP was recorded three consecutive times, and the mean value was adopted. Strict aseptic technique was maintained, and the internal carotid artery, optic nerves, and cavernous sinus were avoided to minimize iatrogenic injury.

Surgical protocol

All endoscopic transsphenoidal tumor resections were performed by the same experienced neurosurgical team using a consistent surgical paradigm, with intraoperative strategies individualized according to tumor load, diaphragmatic tension, and ISP tier. For patients with pituitary apoplexy, complete evacuation of the intratumoral hematoma and necrotic tissue was prioritized to achieve adequate intrasellar decompression, with meticulous dissection to preserve the residual normal pituitary gland and stalk. For high-ISP patients, intrasellar pressure was released in a stepwise, gradual manner to prevent brain shift and traction injury caused by abrupt decompression. Standardized postoperative supportive treatment was applied uniformly: hemostasis, prophylactic anti-infective therapy, dehydration to lower intracranial pressure, and individualized hormone replacement.

Outcome measures

Perioperative clinical indicators. These included the maximal tumor diameter, tumor volume, incidence of preoperative hypopituitarism, intraoperative blood loss, total operative time, postoperative length of stay, and baseline intraoperative ISP. Hypopituitarism was defined as any pituitary hormone level below the lower laboratory reference limit accompanied by corresponding clinical symptoms [18].

Tumor pathological indicators. Postoperative pathological assessment covered the incidence of intratumoral hemorrhage/necrosis, invasive growth status (invasion of the cavernous sinus, diaphragma sellae, or dura confirmed by imaging plus pathology), and the Ki-67 proliferation index, assessed by standardized immunohistochemistry with 1,000 cells counted in proliferative hot spots [19].

Postoperative complications. Major complications included: (1) new-onset hypopituitarism requiring long-term hormone replacement therapy; (2) permanent diabetes insipidus (persisting ≥ 3 months and requiring long-term desmopressin replacement); (3) intracranial infection (a positive CSF culture, or a clinical diagnosis plus ≥ 2 weeks of anti-infective therapy); (4) epistaxis requiring nasal packing,

interventional, or surgical hemostasis within 48 h after surgery; and (5) CSF leak, defined by clear nasal fluid discharge plus a positive β2-transferrin test, or the need for lumbar drainage or secondary repair surgery. Other general complications included transient diabetes insipidus, electrolyte disturbance, and hyposmia.

Postoperative follow-up

All patients underwent structured follow-up for at least 3 months after surgery (outpatient visits plus standardized telephone interviews); all cases lost to follow-up were excluded. Long-term follow-up data beyond 12 months were not collected; analyses of long-term pituitary function and tumor recurrence are therefore limited, as detailed in the Limitations. Assessments included serum pituitary hormone re-examination, contrast-enhanced sellar MRI, and recording of persistent or delayed complications, and were used to evaluate the gross-total resection rate and endocrine functional recovery.

Statistical analysis

All analyses were performed using SPSS 27.0 with two-sided tests ($\alpha = 0.05$). Continuous variables are expressed as the mean ± standard deviation and were compared using independent-samples t tests or one-way analysis of variance with Bonferroni correction (least significant difference test for pairwise comparisons); categorical variables are described as n (%) and were compared using the Pearson χ^2 test or Fisher's exact test when the theoretical frequency was < 5. Independent variables with $P < 0.05$ in the univariate analyses were entered into two separate binary multivariable logistic regression models: Model 1 used "any postoperative complication" and Model 2 used "occurrence of pituitary apoplexy" as the dependent variable. The odds ratio (OR) and 95% confidence interval (CI) were reported; model calibration was evaluated with the Hosmer–Lemeshow goodness-of-fit test ($P > 0.05$ indicating good fit). Receiver operating characteristic (ROC) curves were plotted for all independent risk factors, and the area under the curve (AUC), optimal cutoff value, sensitivity, specificity, and Youden index were calculated; an AUC > 0.7 was considered to indicate good predictive value. Baseline comparisons were used only to describe the balance of clinical characteristics among groups and were not corrected for multiple testing; P values between 0.04 and 0.05 were regarded only as trends toward difference.

Results

Baseline characteristics

A total of 217 patients were enrolled: 46 in the apoplexy group (24 men and 22 women; mean age 48.63 ± 13.89 years) and 171 in the non-apoplexy group (70 men and 101 women; mean age 53.40 ± 18.69 years). Age, sex composition, and body mass index were balanced between the two groups (all $P > 0.05$). The apoplexy group had a significantly greater maximal tumor diameter and tumor volume, higher proportions of nonfunctioning adenomas and hyperprolactinemia, higher incidences of preoperative

adrenal, thyroid, and gonadal axis hypofunction, higher headache visual analogue scale scores, more visual field defects, and a higher prevalence of comorbid hypertension (all $P < 0.05$) (Table 1).

Table 1
Clinical, perioperative, pathological, and complication profiles of the apoplexy and non-apoplexy groups

Baseline characteristics				
Variable	**Apoplexy group (n = 46)**	**Non-apoplexy group (n = 171)**	**t/χ^2 value**	**P value**
Age (years)	**48.63 ± 13.89**	**53.40 ± 18.69**	**1.61**	**0.108**
Male, n (%)	**24 (52.17)**	**70 (40.94)**	**1.86**	**0.17**
BMI (kg/m²)	**24.10 ± 3.54**	**24.80 ± 3.28**	**1.26**	**0.21**
Maximal tumor diameter (mm)	**27.63 ± 10.71**	**24.59 ± 8.20**	**2.08**	**0.04**
Tumor volume (cm³)	**11.34 ± 7.23**	**8.96 ± 5.78**	**2.34**	**0.02**
Suprasellar extension, n (%)	**22 (47.83)**	**86 (50.29)**	**0.09**	**0.77**
Lateral growth, n (%)	**13 (28.26)**	**47 (27.49)**	**0.01**	**0.92**
Knosp grade ≥ 3, n (%)	**25 (54.35)**	**74 (43.27)**	**1.79**	**0.18**
Nonfunctioning tumor, n (%)	**38 (82.61)**	**113 (66.08)**	**4.68**	**0.03**
Hyperprolactinemia, n (%)	**28 (60.87)**	**64 (37.43)**	**8.16**	**< 0.01**
Preoperative adrenal axis insufficiency, n (%)	**30 (65.22)**	**46 (26.90)**	**23.39**	**< 0.01**
Preoperative hypothyroidism, n (%)	**16 (34.78)**	**32 (18.71)**	**5.43**	**0.02**
Preoperative hypogonadism, n (%)	**18 (39.13)**	**36 (21.05)**	**6.34**	**0.01**
Headache VAS score (points)	**6.55 ± 2.34**	**4.32 ± 2.56**	**5.34**	**< 0.01**
Visual field defect, n (%)	**27 (58.70)**	**54 (31.58)**	**11.39**	**< 0.01**
Comorbid hypertension, n (%)	**24 (52.17)**	**58 (33.92)**	**5.14**	**0.02**
Intraoperative and perioperative outcomes				
Gross-total resection, n (%)	35 (76.09)	152 (88.89)	4.99	0.03
Complete diaphragmatic descent, n (%)	32 (69.57)	145 (84.80)	5.59	0.02
Intraoperative blood loss (mL)	324.58 ± 153.77	279.86 ± 105.44	2.30	0.02
Operative time (h)	2.63 ± 0.69	2.24 ± 1.01	2.47	0.01

Note: Univariate comparisons were not corrected for multiple testing; borderline P values (0.04–0.05) are provided for descriptive reference only. BMI body mass index, VAS visual analogue scale, ISP intrasellar pressure, CSF cerebrospinal fluid.

Baseline characteristics				
Variable	**Apoplexy group (n = 46)**	**Non-apoplexy group (n = 171)**	**t/χ² value**	**P value**
Age (years)	**48.63 ± 13.89**	**53.40 ± 18.69**	**1.61**	**0.108**
Length of hospital stay (d)	10.55 ± 3.43	8.66 ± 2.31	4.40	< 0.01
Cerebrospinal fluid leak, n (%)	11 (23.91)	19 (11.11)	4.99	0.03
Intraoperative ISP (mmHg)	25.36 ± 5.66	20.44 ± 8.23	3.82	< 0.01
Pathological characteristics				
Tumor necrosis, n (%)	46 (100.00)	25 (14.62)	120.04	< 0.01
Intratumoral hemorrhage, n (%)	46 (100.00)	0 (0.00)	217.00	< 0.01
Invasive tumor, n (%)	27 (58.70)	72 (42.11)	4.02	0.04
Ki-67 proliferation index (%)	3.83 ± 1.25	2.19 ± 0.92	9.89	< 0.001
Postoperative complications				
Permanent diabetes insipidus, n (%)	4 (8.70)	2 (1.17)	5.09	0.02
New-onset hypopituitarism, n (%)	10 (21.74)	17 (9.94)	4.63	0.03
Intracranial infection, n (%)	2 (4.35)	6 (3.51)	0.09	0.76
Epistaxis, n (%)	2 (4.35)	3 (1.75)	0.24	0.63
Cerebrospinal fluid leak, n (%)	5 (10.87)	4 (2.34)	4.66	0.03
Electrolyte disturbance, n (%)	12 (26.09)	40 (23.39)	0.14	0.70
Hyposmia, n (%)	5 (10.87)	14 (8.19)	0.08	0.78
Transient diabetes insipidus, n (%)	16 (34.78)	32 (18.71)	5.43	0.02

Note: Univariate comparisons were not corrected for multiple testing; borderline P values (0.04–0.05) are provided for descriptive reference only. BMI body mass index, VAS visual analogue scale, ISP intrasellar pressure, CSF cerebrospinal fluid.

Across the three ISP tiers, age, sex, and body mass index did not differ significantly (all P > 0.05). The high-ISP group showed a significantly greater tumor load and higher proportions of suprasellar extension and Knosp grade ≥ 3 cavernous sinus invasion, and the incidences of pituitary apoplexy, preoperative panhypopituitarism, severe headache, visual impairment, and comorbid hypertension were all significantly higher than in the intermediate- and low-ISP groups (all P < 0.05) (Table 2).

Table 2
Clinical, perioperative, pathological, and complication profiles of patients stratified by intrasellar pressure (ISP) tier

Baseline characteristics					
Variable	**G1 (ISP < 15 mmHg, n = 42)**	**G2 (ISP 15–24 mmHg, n = 109)**	**G3 (ISP ≥ 25 mmHg, n = 66)**	**F/χ^2 value**	**P value**
Age (years)	**52.36 ± 14.87**	**51.95 ± 12.65**	**53.15 ± 12.69**	**0.17**	**0.84**
Male, n (%)	**15 (35.71)**	**51 (46.79)**	**28 (42.42)**	**1.55**	**0.46**
BMI (kg/m²)	**23.31 ± 3.22**	**24.23 ± 2.57**	**23.73 ± 2.01**	**2.14**	**0.12**
Maximal tumor diameter (mm)	**16.46 ± 5.22**	**24.54 ± 8.33***	**29.12 ± 10.23*†**	**28.60**	**< 0.01**
Tumor volume (cm³)	**4.34 ± 2.05**	**8.89 ± 3.74***	**12.08 ± 5.57*†**	**44.52**	**< 0.01**
Suprasellar extension, n (%)	**10 (23.81)**	**58 (53.21)***	**40 (60.61)***	**14.94**	**< 0.01**
Lateral growth, n (%)	**8 (19.05)**	**33 (30.28)**	**19 (28.79)**	**1.97**	**0.37**
Knosp grade ≥ 3, n (%)	**6 (14.29)**	**53 (48.62)***	**40 (60.61)***	**22.99**	**< 0.01**
Pituitary apoplexy, n (%)	**6 (14.29)**	**18 (16.51)**	**22 (33.33)*†**	**8.45**	**0.01**
Nonfunctioning tumor, n (%)	**23 (54.76)**	**78 (71.56)***	**50 (75.76)***	**5.75**	**0.06**
Hyperprolactinemia, n (%)	**12 (28.57)**	**40 (36.70)**	**34 (51.52)***	**6.44**	**0.04**
Preoperative adrenal axis insufficiency, n (%)	**9 (21.43)**	**34 (31.19)**	**33 (50.00)*†**	**10.62**	**< 0.01**
Preoperative hypothyroidism, n (%)	**6 (14.29)**	**20 (18.35)**	**22 (33.33)*†**	**7.21**	**0.03**
Preoperative hypogonadism, n (%)	**7 (16.67)**	**27 (24.77)**	**26 (39.39)*†**	**7.53**	**0.02**
Headache VAS score (points)	**3.36 ± 1.29**	**4.88 ± 2.26***	**6.75 ± 3.08*†**	**26.95**	**< 0.01**
Visual field defect, n (%)	**11 (26.19)**	**37 (33.94)**	**33 (50.00)*†**	**7.29**	**0.03**

* P < 0.05 vs. the G1 group; † P < 0.05 vs. the G2 group. F values (ANOVA) were used for continuous variables and χ^2 values for categorical variables. Univariate comparisons were not corrected for multiple testing; borderline P values are provided for descriptive reference only. G1: ISP < 15 mmHg; G2: 15–24 mmHg; G3: ≥ 25 mmHg.

Baseline characteristics					
Variable	**G1 (ISP < 15 mmHg, n = 42)**	**G2 (ISP 15–24 mmHg, n = 109)**	**G3 (ISP ≥ 25 mmHg, n = 66)**	**F/χ² value**	**P value**
Age (years)	**52.36 ± 14.87**	**51.95 ± 12.65**	**53.15 ± 12.69**	**0.17**	**0.84**
Comorbid hypertension, n (%)	**14 (33.33)**	**34 (31.19)**	**34 (51.52)†**	**7.66**	**0.02**
Intraoperative and perioperative outcomes					
Gross-total resection, n (%)	40 (95.24)	99 (90.83)	48 (72.73)*†	14.89	< 0.01
Complete diaphragmatic descent, n (%)	41 (97.62)	90 (82.57)*	46 (69.70)*†	13.46	< 0.01
Intraoperative blood loss (mL)	168.50 ± 58.24	245.36 ± 65.71*	368.74 ± 82.40*†	116.69	< 0.01
Operative time (h)	2.11 ± 0.65	2.82 ± 1.04*	3.20 ± 1.19*†	14.48	< 0.01
Length of hospital stay (d)	7.83 ± 1.50	9.69 ± 1.98*	13.22 ± 2.77*†	90.42	< 0.01
Cerebrospinal fluid leak, n (%)	2 (4.76)	13 (11.93)	15 (22.73)*	7.62	0.02
Pathological characteristics					
Tumor necrosis, n (%)	8 (19.05)	15 (13.76)	23 (34.85)†	11.09	< 0.01
Intratumoral hemorrhage, n (%)	8 (19.05)	16 (14.68)	22 (33.33)†	8.71	0.01
Invasive growth, n (%)	12 (28.57)	43 (39.45)	44 (66.67)*†	18.38	< 0.01
Ki-67 proliferation index (%)	1.55 ± 0.44	2.31 ± 0.52*	2.76 ± 0.91*†	44.23	< 0.01
Postoperative complications					
Permanent diabetes insipidus, n (%)	0 (0.00)	1 (0.92)	5 (7.58)	8.26	0.02
New-onset hypopituitarism, n (%)	2 (4.76)	11 (10.09)	14 (21.21)*†	7.49	0.02
Intracranial infection, n (%)	0 (0.00)	3 (2.75)	5 (7.58)	4.69	0.10
Epistaxis, n (%)	0 (0.00)	2 (1.83)	3 (4.55)	2.57	0.28

* P < 0.05 vs. the G1 group; † P < 0.05 vs. the G2 group. F values (ANOVA) were used for continuous variables and χ^2 values for categorical variables. Univariate comparisons were not corrected for multiple testing; borderline P values are provided for descriptive reference only. G1: ISP < 15 mmHg; G2: 15–24 mmHg; G3: ≥ 25 mmHg.

Baseline characteristics					
Variable	**G1 (ISP < 15 mmHg, n = 42)**	**G2 (ISP 15–24 mmHg, n = 109)**	**G3 (ISP ≥ 25 mmHg, n = 66)**	**F/χ² value**	**P value**
Age (years)	**52.36 ± 14.87**	**51.95 ± 12.65**	**53.15 ± 12.69**	**0.17**	**0.84**
Cerebrospinal fluid leak, n (%)	0 (0.00)	3 (2.75)	6 (9.09)	6.41	0.04
Electrolyte disturbance, n (%)	10 (23.81)	24 (22.02)	18 (27.27)	0.62	0.73
Hyposmia, n (%)	1 (2.38)	10 (9.17)	8 (12.12)	3.10	0.21
Transient diabetes insipidus, n (%)	4 (9.52)	23 (21.10)	21 (31.82)*	7.54	0.02

* P < 0.05 vs. the G1 group; † P < 0.05 vs. the G2 group. F values (ANOVA) were used for continuous variables and χ² values for categorical variables. Univariate comparisons were not corrected for multiple testing; borderline P values are provided for descriptive reference only. G1: ISP < 15 mmHg; G2: 15–24 mmHg; G3: ≥ 25 mmHg.

Intraoperative, perioperative, and pathological indicators

Intraoperative blood loss, operative time, length of hospital stay, intraoperative ISP, and the incidence of CSF leak were significantly higher in the apoplexy group than in the non-apoplexy group, whereas the gross-total resection rate and the complete diaphragmatic descent rate were significantly lower (all P < 0.05). All specimens in the apoplexy group showed intratumoral hemorrhage and necrotic foci, and the proportion of invasive tumors and the Ki-67 proliferation index were significantly higher than in the non-apoplexy group (all P < 0.05) (Table 1).

With increasing ISP, intraoperative blood loss progressively increased, operative time and hospital stay lengthened, and the risk of CSF leak rose, whereas the rates of gross-total resection and complete diaphragmatic descent declined in a gradient manner; the incidences of intratumoral hemorrhage, necrosis, and invasive growth, as well as the Ki-67 index, increased stepwise with ISP (all P < 0.05) (Table 2).

Postoperative complications

The incidences of diabetes insipidus, new-onset hypopituitarism, and CSF leak were significantly higher in the apoplexy group (all P < 0.05), whereas intracranial infection, epistaxis, electrolyte disturbance, and hyposmia did not differ significantly between the two groups (all P > 0.05). Similarly, only the incidences of diabetes insipidus, new-onset hypopituitarism, and CSF leak increased in a gradient with rising ISP, whereas the other complications did not differ significantly among the three ISP tiers (all P > 0.05) (Tables 1 and 2).

Independent risk factors and predictive performance

Multivariable logistic regression for postoperative complications. The Hosmer–Lemeshow test of the binary regression model for postoperative complications yielded $\chi^2 = 3.278$ and $P = 0.773$, indicating a good model fit. Pituitary apoplexy, ISP ≥ 25 mmHg, invasive tumor growth, Ki-67 ≥ 3%, intraoperative blood loss ≥ 300 mL, and maximal tumor diameter ≥ 3 cm were all independent risk factors for postoperative complications (all $P < 0.05$) (Table 3).

Table 3
Multivariable logistic regression analysis of risk factors for postoperative complications and pituitary apoplexy

Model 1: independent risk factors for postoperative complications (Hosmer–Lemeshow $\chi^2 = 3.278$, $P = 0.773$)						
Independent variable	**β**	**SE**	**Wald χ^2**	**OR**	**95% CI**	**P value**
Pituitary apoplexy	**2.571**	**1.224**	**4.409**	**13.075**	**1.187–144.068**	**0.036**
High ISP (ISP ≥ 25 mmHg)	**1.976**	**0.821**	**5.801**	**7.217**	**1.445–36.048**	**0.016**
Invasiveness (Knosp grade ≥ 3)	**1.664**	**0.758**	**4.811**	**5.278**	**1.194–23.337**	**0.028**
Ki-67 proliferation index (≥ 3%)	**2.272**	**0.763**	**8.863**	**9.701**	**2.173–43.304**	**0.003**
Intraoperative blood loss (≥ 300 mL)	**2.881**	**0.759**	**14.406**	**17.829**	**4.028–78.924**	**< 0.001**
Maximal tumor diameter (≥ 3 cm)	**3.277**	**0.884**	**13.755**	**26.498**	**4.689–149.739**	**< 0.001**
Model 2: independent risk factors for pituitary apoplexy (Hosmer–Lemeshow $\chi^2 = 5.035$, $P = 0.284$)						
High ISP (ISP ≥ 25 mmHg)	3.607	0.615	34.421	36.862	11.047–123.007	< 0.001
Hypertension	1.116	0.547	4.167	3.053	1.046–8.916	0.041
Hyperprolactinemia	2.360	0.581	16.473	10.591	3.388–33.103	< 0.001

SE standard error, OR odds ratio, CI confidence interval, ISP intrasellar pressure.

ROC analysis for postoperative complications. All six independent predictors had AUCs > 0.7 (all $P < 0.001$). The Ki-67 index showed the best predictive performance (AUC = 0.844, Youden index 0.689), followed by high ISP (AUC = 0.834, Youden index 0.669); these can be used for the rapid screening of extremely high-risk populations (Table 4, Fig. 1).

Table 4
Predictive performance of clinical indicators for postoperative complications and pituitary apoplexy (ROC analysis)

Predictive performance for postoperative complications							
Predictor	**AUC**	**SE**	**95% CI**	**P value**	**Sensitivity (%)**	**Specificity (%)**	**Youden index**
Pituitary apoplexy	**0.789**	**0.037**	**0.717–0.861**	**< 0.001**	**58.4**	**99.3**	**0.577**
High ISP (ISP ≥ 25 mmHg)	**0.834**	**0.032**	**0.771–0.898**	**< 0.001**	**74.0**	**92.9**	**0.669**
Maximal tumor diameter (≥ 3 cm)	**0.794**	**0.033**	**0.730–0.858**	**< 0.001**	**83.1**	**75.7**	**0.588**
Ki-67 proliferation index (≥ 3%)	**0.844**	**0.032**	**0.782–0.907**	**< 0.001**	**75.3**	**93.6**	**0.689**
Invasiveness (Knosp grade ≥ 3)	**0.783**	**0.033**	**0.719–0.848**	**< 0.001**	**83.1**	**73.6**	**0.567**
Intraoperative blood loss(≥ 300 mL)	**0.826**	**0.031**	**0.766–0.887**	**< 0.001**	**83.1**	**82.1**	**0.652**
Predictive performance for pituitary apoplexy							
High ISP (ISP ≥ 25 mmHg)	0.889	0.028	0.833–0.945	< 0.001	91.3	86.5	0.778
Hypertension	0.726	0.042	0.643–0.810	< 0.001	73.9	71.3	0.452
Hyperprolactinemia	0.783	0.036	0.712–0.854	< 0.001	87.0	69.6	0.566
AUC area under the curve, SE standard error, CI confidence interval, ISP intrasellar pressure.							

Multivariable logistic regression for pituitary apoplexy. The Hosmer–Lemeshow test yielded $\chi^2 = 5.035$ and P = 0.284, meeting the standard for model fit. High ISP (ISP ≥ 25 mmHg), hypertension, and hyperprolactinemia were independent risk factors for pituitary apoplexy (all P < 0.01) (Table 3).

ROC analysis for pituitary apoplexy. High ISP predicted pituitary apoplexy with an AUC of 0.889, significantly outperforming hypertension (AUC = 0.726) and hyperprolactinemia (AUC = 0.783) (all P < 0.001) (Table 4, Fig. 2).

Discussion

Using a consecutive cohort of 217 patients undergoing primary endoscopic transsphenoidal surgery, this study performed stratified comparisons according to apoplexy status and three intraoperative ISP tiers and clarified—through multivariable regression and ROC prediction models—the central role of intrasellar

pressure as a quantifiable mechanical indicator linking tumor mass effect, pituitary apoplexy, tumor proliferative-invasive phenotypes, and postoperative complications. Three findings are of particular clinical relevance. First, ISP ≥ 25 mmHg is an independent risk factor for pituitary apoplexy with an AUC of 0.889, markedly outperforming hypertension and hyperprolactinemia. Second, ISP ≥ 25 mmHg is also an independent predictor of postoperative complications, together with apoplexy, invasive growth, Ki-67 ≥ 3%, blood loss ≥ 300 mL, and tumor diameter ≥ 3 cm. Third, perioperative outcomes worsen in a stepwise gradient across ISP tiers, providing a rationale for tiered perioperative endocrine monitoring.

The phenotypic differences between apoplectic and non-apoplectic patients are mechanistically coherent. Nonfunctioning adenomas lack specific hormonal symptoms at an early stage; their prolonged occult growth crowds the limited intrasellar space, subjecting microvessels to chronic compression, while concurrent hypertension and hyperprolactinemia further impair the already tenuous tumor microcirculation, ultimately precipitating acute hemorrhage [23–25, 27]. Intraoperatively, apoplectic lesions form a mixed solid–necrotic hematoma structure with blurred boundaries between the tumor and the residual gland, so hematoma evacuation inevitably increases the risk of vascular and diaphragmatic injury. Postoperatively, the apoplectic mass acutely compresses the pituitary stalk and anterior lobe, an effect compounded by the mechanical trauma of hematoma evacuation, ultimately resulting in significantly increased incidences of diabetes insipidus and new-onset permanent hypopituitarism. The mean age of the apoplexy group was numerically lower than that of the non-apoplexy group, apparently at variance with studies identifying advanced age as a risk factor; this is explained by the enrollment of only symptomatic apoplexy requiring surgery—elderly patients with asymptomatic subclinical hemorrhage carry no surgical indication and were not captured—and by the faster proliferation and more fragile neovascular walls of functioning adenomas in younger patients, allowing ISP to breach 25 mmHg abruptly. Consistently, multivariable regression confirmed that age was not an independent risk factor.

The evolution from our group's previous negative conclusion [14] to the present strongly positive one (OR = 36.862, AUC = 0.889) is attributable to three methodological improvements rather than to data fluctuation. First, statistical power: the previous cohort contained only 17 apoplexy events, yielding an events-per-variable ratio below 3:1, whereas the present 46 events provide a ratio exceeding 7:1. Second, threshold refinement: the previous exploratory analysis used a non-validated 20-mmHg cutoff, whereas the present study adopted the internationally recognized 15/25-mmHg three-tier scheme [13, 17]. Third, stricter diagnostic criteria: the previous dual standard may have included asymptomatic subclinical micro-hemorrhage, whereas the present clinical–imaging–pathological triple standard improves the specificity of apoplexy determination. This comparison itself corroborates that insufficient sample size was the primary reason for the earlier negative conclusion.

The gradient relationships observed here are highly consistent with the consecutive endoscopic cohorts of the Simander group [12, 13], which likewise demonstrated increased intratumoral hemorrhage, pituitary dysfunction, and postoperative CSF leak in high-ISP patients. Mechanistically, giant invasive suprasellar tumors expand the intrasellar compartment and raise static ISP, while sustained high ISP

causes intratumoral microcirculatory stasis and chronic hypoxia, forming a self-amplifying vicious cycle of tumor expansion → elevated ISP → hypoxic necrosis → aberrant vascular proliferation → further enlargement and hemorrhage [28]. The incidence of apoplexy in the high-ISP group reached 33.33%, more than twice that of the low-ISP group (14.29%), and pathological indicators worsened stepwise with ISP, matching the mechanism of hypoxia-induced tumor-promoting pathways. Postoperative endocrine complications followed an entirely consistent ISP-gradient pattern, whereas complications unrelated to the diaphragma sellae or pituitary anatomy were unaffected by ISP, indicating that high intrasellar pressure injures specifically the pituitary–stalk–diaphragm structures.

The independent risk factors identified for the two outcomes correspond to distinct pathogenic dimensions: local mechanical load (ISP ≥ 25 mmHg), systemic hemodynamic background (hypertension), and tumor endocrine regulation (hyperprolactinemia) for apoplexy; and anatomy (diameter ≥ 3 cm, invasive growth), proliferation (Ki-67 ≥ 3%), operative injury (blood loss ≥ 300 mL), and intrasellar mechanical/apoplectic status for complications [29–31]. The Ki-67 index and ISP stratification were the best predictors of complications (AUCs of 0.844 and 0.834, respectively), and apoplexy showed a specificity approaching 99%; these quantitative indicators can be integrated into a standardized perioperative risk stratification system guiding individualized surgical plans and monitoring intensity.

The clinical translational value is threefold. Preoperatively, patients with hypertension, hyperprolactinemia, or giant adenomas can be flagged for intraoperative ISP quantification, with pre-emptive blood pressure control and standardized prolactin lowering to avert acute apoplexy. Intraoperatively, high-ISP and apoplexy patients warrant stepwise slow intrasellar decompression to avoid brain shift, prophylactic multilayer diaphragmatic reconstruction to reduce CSF leak, and meticulous subcapsular dissection to preserve residual pituitary tissue. Postoperatively, patients with apoplexy, ISP ≥ 25 mmHg, Ki-67 ≥ 3%, or giant invasive adenomas require extended urine output, electrolyte, and pituitary hormone monitoring with early hormone replacement to reduce permanent endocrine damage.

This study has several limitations. It was a single-center retrospective cohort, entailing selection bias; multicenter prospective validation is needed. The follow-up period was at least 3 months but lacked systematic data beyond 12 months, precluding analysis of long-term pituitary function and tumor recurrence. Only primary tumors were included, so the conclusions do not apply to recurrent or post-radiochemotherapy cases. As an observational study, it cannot clarify the effects of different intraoperative decompression protocols in high-ISP patients; prospective interventional studies are warranted to optimize the decompression paradigm.

Conclusions

Patients with pituitary apoplexy exhibit a greater tumor load and proliferative-invasive activity, greater intraoperative trauma, and significantly increased risks of diabetes insipidus, new-onset hypopituitarism,

and CSF leak. Intrasellar pressure is the key mediating indicator connecting tumor mass effect, the onset of apoplexy, and adverse postoperative outcomes: the higher the ISP, the higher the risks of tumor necrosis, hemorrhage, and invasive proliferation, with a gradient increase in postoperative endocrine and diaphragm-related complications. High ISP (≥ 25 mmHg), hypertension, and hyperprolactinemia independently predict apoplexy, whereas apoplexy, high ISP, invasive growth, Ki-67 ≥ 3%, blood loss ≥ 300 mL, and tumor diameter ≥ 3 cm independently predict postoperative complications. Real-time intraoperative ISP monitoring, combined with blood pressure, prolactin, imaging, and pathological indicators, can support comprehensive preoperative risk stratification; for high-risk patients, pharmacological preconditioning, gradual decompression with diaphragmatic protection, and intensified postoperative endocrine monitoring can reduce apoplexy and complications.

Declarations

Competing interests:

The authors declare that they have no competing interests.

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Bengbu Medical University (approval No. 2022KY064) and was conducted in accordance with the Declaration of Helsinki and its later amendments. The requirement for written informed consent was waived because of the retrospective design based on de-identified archived data.

Consent for publication:

Not applicable.

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Author Contribution

Zhiquan Jiang and Xialin Zheng conceived and designed the study and performed the intraoperative ISP measurements. Dongqi Shao and Yu Li reviewed and revised the manuscript. Rui Xu and Chenxi Li collected the clinical data. Shan Xie and Zhilin Shao conducted the study and wrote the paper. All authors read and approved the final manuscript.

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Data availability:

The datasets generated and analyzed during the current study are available from the corresponding authors on reasonable request.

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Figures

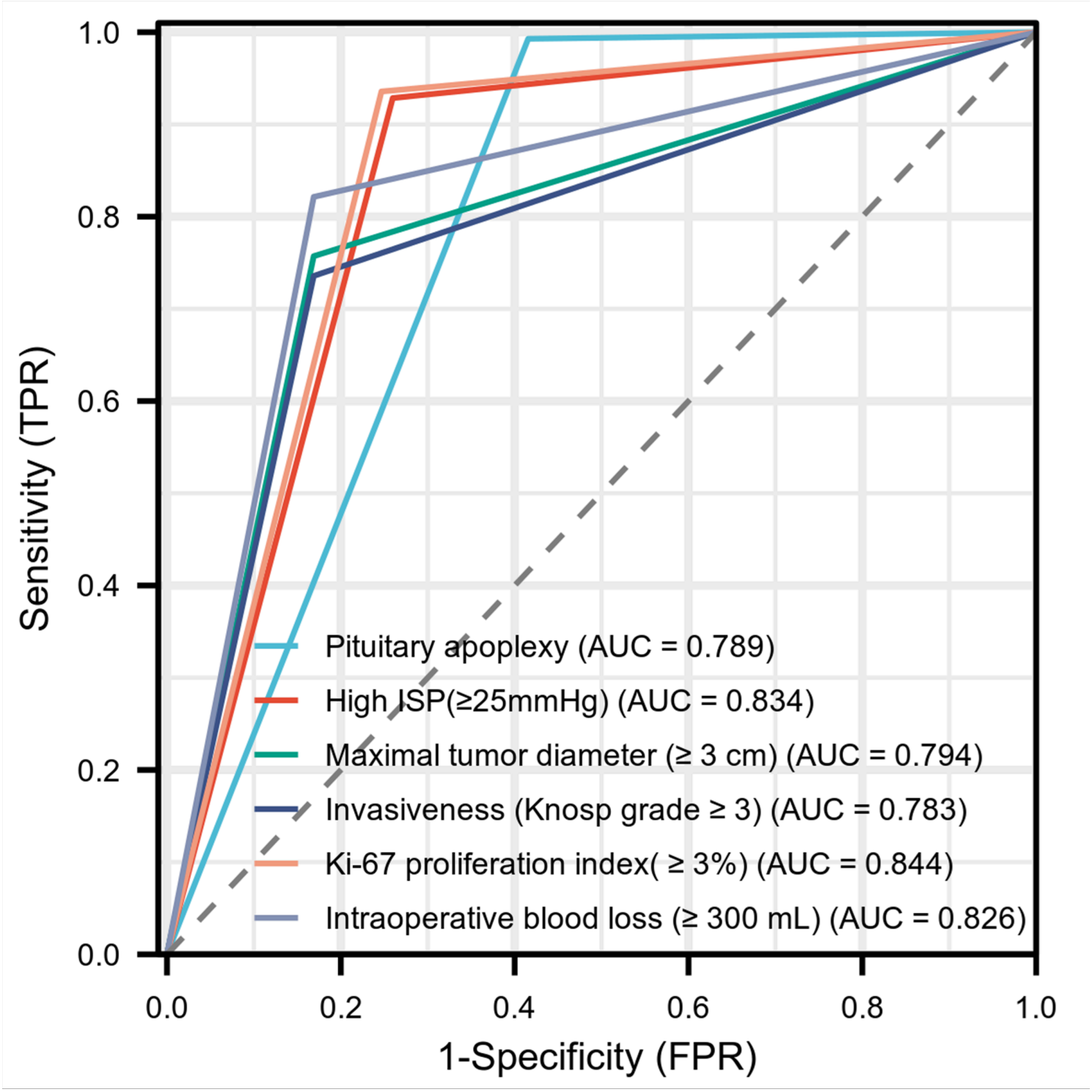


Figure 1

Receiver operating characteristic (ROC) curves of clinical indicators for predicting postoperative complications.

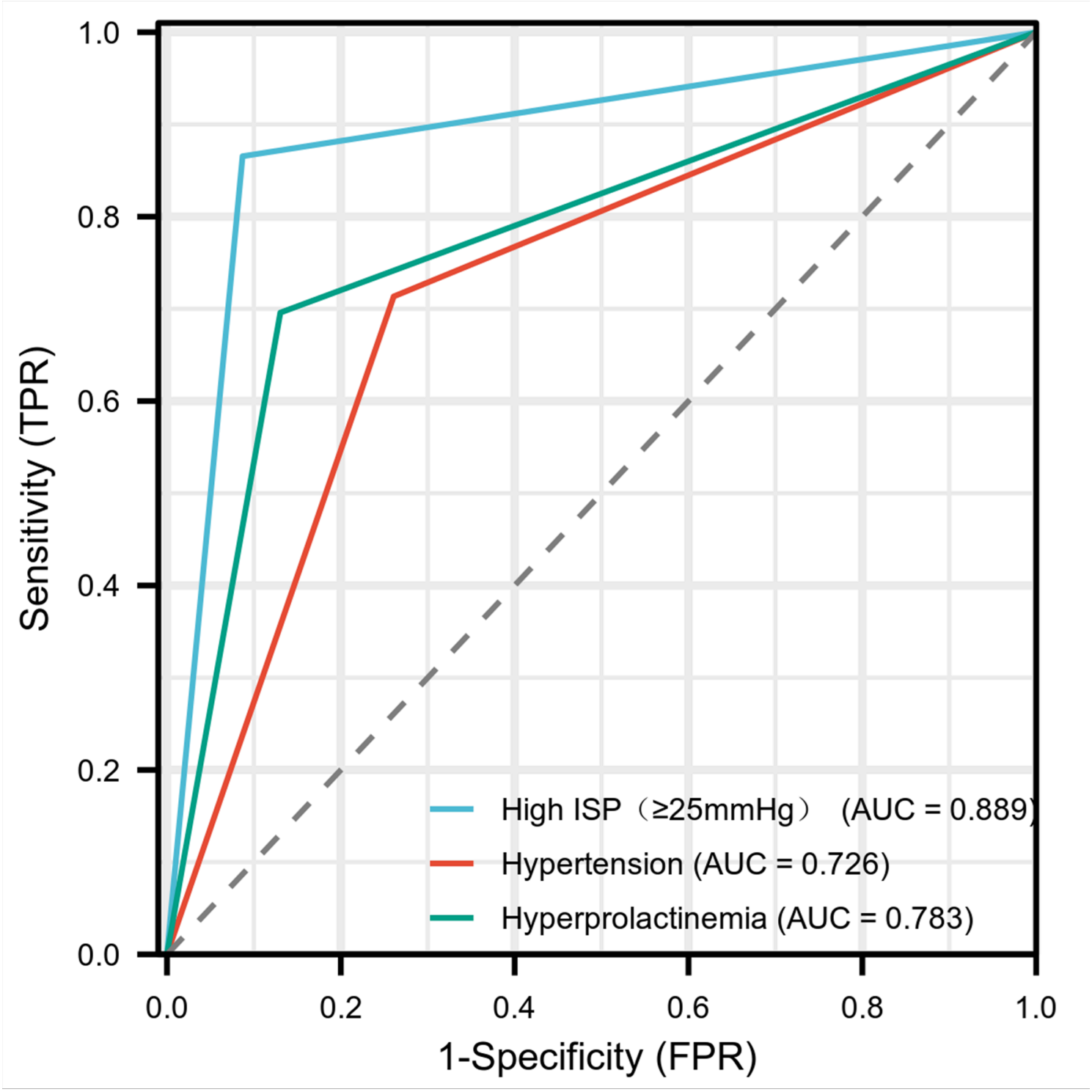


Figure 2

Receiver operating characteristic (ROC) curves of clinical indicators for predicting pituitary apoplexy.