RESEARCH

Severe hypernatremia during postoperative care in patients with craniopharyngioma

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Abstract

Purpose: We aimed to describe and predict the risk of severe hypernatremia after surgical resection of craniopharyngioma and to identify the association of water intake, urine output, and sodium level change in the patients.
Method: The outcome was postoperative severe hypernatremia. We identified risk factors associated with hypernatremia using multivariable regression. We trained machine learning models to predict the outcome. We compared serum sodium change, intravenous input, oral input, total input, urine output, and net fluid balance according to different nurse shifts.
Results: Among 234 included patients, 125 developed severe hypernatremia after surgery. The peak incidence occurred during day 0 and day 6 after surgery. The risk was increased in patients with gross total resection (odds ratio (OR) 2.41, $P < 0.001$), high Puget classification (OR 4.44, $P = 0.026$), preoperative adrenal insufficiency (OR 2.01, $P = 0.040$), and preoperative hypernatremia (OR 5.55, $P < 0.001$). The random forest algorithm had the highest area under the receiver operating characteristic curve (0.770, 95% CI, 0.727–0.813) in predicting the outcome and was validated in the prospective validation cohort. Overnight shifts were associated with the highest serum sodium increase ($P = 0.010$), less intravenous input ($P < 0.001$), and less desmopressin use ($P < 0.001$).
Conclusion: The overall incidence of severe hypernatremia after surgical resection of craniopharyngioma was significant, especially in patients with gross total resection, hypothalamus distortion, preoperative adrenal insufficiency, and preoperative severe hypernatremia. Less intravenous input and less desmopressin use were associated with serum sodium increases, especially during overnight shifts.

Keywords

- electrolyte disturbance
- neurosurgery
- nursing
- craniopharyngioma

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Introduction

Craniopharyngioma is an intracranial neoplasm that originates from the remnant of the craniopharyngeal duct. The tumor is located in the hypothalamic–pituitary region and is closely related to important structures such as the pituitary gland, pituitary stalk, and optic chiasm. Some tumors invade adjacent brain tissue, such as the hypothalamus and the third ventricle. Treatment of craniopharyngioma focuses as much as possible on neurosurgery (transcranial or transsphenoidal approach). However, most patients have a risk of developing arginine vasopressin deficiency after surgery (1, 2). Therefore, sufficient hydration is needed to maintain fluid balance. In some cases, however, negative fluid balances still occur. The most common surgical complication in these patients is electrolyte disturbance characterized by hypernatremia (3). Previous studies have estimated the prevalence of hypernatremia in patients with craniopharyngioma to be between 15% and 44.8% (4, 5).

Correct prediction of postoperative hypernatremia can alert the postoperative nursing team to initiate preventive procedures (such as providing adequate hydration and frequent monitoring) and potentially reduce the risk of hypernatremia. In recent years, the use of machine learning to build predictive models has become increasingly popular in medical research. Its advantages involve automatic selection of information variables, capturing nonlinear relationships among variables, and improving predictive ability (6). The main purpose of the present study was to establish and validate a model for predicting hypernatremia after craniopharyngioma resection.

As mentioned, patients with craniopharyngioma often develop persistent arginine vasopressin deficiency. We hypothesize that inadequate intake of water is the primary cause of hypernatremia in these patients. A secondary purpose of the study was to determine the relationship between water intake, urine output, and sodium level change in these patients.

Methods

This study was approved by the institutional review board of Huashan Hospital. We used the Gold Pituitary Database, in which patients provided informed consent when their records were entered. The database went online in January 2021, with support for multidimensional queries (Hospital Information System, Laboratory Information System, Picture Archiving, Communication Systems, and other systems linked to institutions through unique identifiers) and real-world analysis. Data for patients treated before the database deployment were retrospectively collected and those for patients treated after the database deployment were collected prospectively. This study followed the Transparent Reporting of multivariable Prediction Models for Individual Prognosis or Diagnosis (TRIPOD) guideline, provided in the Appendix.

We included consecutive patients with craniopharyngioma surgically treated at the Huashan Hospital West Campus from January 2019 to December 2021. Patients treated from January 2019 to December 2020 and from January 2021 to December 2021 served as the training cohort and the validation cohort, respectively. We excluded those patients who were aged less than 18 years.

Postoperative steroid regime was similar across the cohort, including intravenous methylprednisolone followed by oral cortisone. After surgery, we monitored serum electrolytes every morning. In patients with severe hypernatremia, serum electrolytes were measured in the afternoon, if necessary. Patients with hypernatremia can be treated with saline, hypotonic saline, or oral water, depending on their serum sodium level. The consecutive days of hypernatremia were recorded.

For the first study aim, the outcome was postoperative severe hypernatremia, defined as serum sodium level higher than 150 mmol/L after surgery. We used multivariable logistic regression to investigate possible risk factors for severe hypernatremia. These predictors included age, sex, symptoms (headache, visual disturbance, polyuria, weakness), tumor diameter, tumor type (intrasellar, suprasellar, or third ventricular), calcification, Puget classification (free of hypothalamus contact, hypothalamus contact, or hypothalamus distortion), and surgical findings (approach, stalk preservation, and resection extent). Laboratory variables included preoperative serum sodium, cortisol, thyroxine, and free thyroxine. To avoid bias during data entry, investigators were blinded to the predictors and outcome using natural language processing and an automatic extraction technique.

All patients underwent standardized endocrine assessment at our center prior to surgery. Patients with a morning cortisol level of less than 3 mg/mL were considered to have central adrenal insufficiency, and patients with a morning cortisol level of more

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than 15 mg/mL were considered normal. Patients with morning cortisol levels between 3 and 15 mg/dL were tested using an adrenocorticotropic hormone stimulation test or insulin tolerance test, with a peak cortisol value < 18 mg/dL defined as central adrenal insufficiency. Central hypothyroidism was diagnosed with serum free thyroxine level below the reference value and insufficient thyroid hormone levels. Clinical presentation, urine specific gravity, urine and serum osmolality, serum sodium level, and a need for desmopressin treatment were comprehensively evaluated for the diagnosis of central arginine vasopressin deficiency.

We developed models to predict postoperative hypernatremia. In the training cohort, we used regression (logistic regression, penalized logistic regression) and developed machine learning algorithms (support vector machine, linear discriminant analysis, random forest, gradient boost machine, and an ensemble algorithm) to predict the outcome. The model performance was assessed in 5-fold cross-validation, in which the dataset was randomly divided into five even groups and evaluation was performed on one group at a time using the model built on the remaining 80% of the data. The algorithms with the highest c-statistic (area under receiver operating characteristic curve, AUC) were chosen as the best model, which was further validated in the validation cohort.

The calibration of the model was evaluated using calibrated intercept and calibrated slope. Patients were further classified into low, medium, and high risk using 0.33 and 0.67 as the cutoff value, and the risk of hypernatremia was calculated for each group. Feature importance was calculated to further analyze the association between patient characteristics and model outcomes. We developed a nomogram that allows interaction to explore the impact of risk factors and their combinations on outcomes. The choice of variables for the nomogram was based on essential features ranked according to feature importance.

To achieve the second study aim, we investigated the relationship between diurnal fluid balance and sodium change. The time frame was divided into 08:00–16:00, 16:00–24:00, and 24:00–08:00 h, corresponding to the day shift, night shift, and overnight shift of the nursing team. First, we recorded intravenous input, oral input, and urine output in every shift. Total input equals oral input plus intravenous input. Net fluid balance equals total input minus urine output. We calculated the mean sodium change during every shift by averaging the change between the two nearest time frames. We compared intravenous input, oral input, total input, urine output, and net fluid balance according to different shifts.

Descriptive statistics were obtained for all the available data. The statistical significance between two groups for continuous variables was determined using the Student's *t*-test. Other continuous variables were analyzed using nonparametric tests (Mann–Whitney *U* test). Categorical variables were analyzed using a chi-squared test or Fisher's exact test, as appropriate. R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis and model creation.

Results

We included 234 consecutive patients with craniopharyngioma, after the exclusion of 18 patients less than 18 years old. Among them, 186 patients were treated before database deployment and served as the training group; data for the remaining 48 patients were collected prospectively and served as the validation group. In the training cohort, 57.5% were male, 22.6% had previous surgery, and the majority cases were performed by transsphenoidal approach. Table 1 presents the similar distribution of baseline characteristics between the training and validation cohorts.

The highest mean serum sodium level was observed on the operation day (day 0, 147 mmol/L), which gradually reduced afterward (Fig. 1). The peak incidence was during day 0 and day 6 after surgery. Between day 6 and day 9, there was an episode of increased hyponatremia. In general, 125 patients (53.4%) had at least one measurement of severe hypernatremia after surgery, and 52 patients (22.2%) had severe hypernatremia for more than 3 consecutive days. 8.6% of the patients developed at least one measure of hyponatremia after surgery.

In the multivariable analysis (Table 2), the incidence of severe hypernatremia was increased in patients with gross total resection (odds ratio (OR) 2.41, $P < 0.001$) and in patients with high Puget classification (OR 4.44, $P = 0.026$). Preoperative adrenal insufficiency (OR 2.01, $P = 0.040$) and severe hypernatremia (OR 5.55, $P < 0.001$) were also associated with an increased risk of postoperative severe hypernatremia in the multivariable analysis. For the prolonged duration of postoperative severe hypernatremia, in addition

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Table 1 Characteristics between training cohort and validation cohort.

	Training cohort (n = 186)	Validation cohort (n = 48)	P
Age (years)	43.7 (15.2)	40.7 (16.6)	0.230
Gender (male)	107 (57.5%)	22 (45.8%)	0.197
Radiotherapy history	6 (3.2%)	2 (4.2%)	1.000
Surgical history	42 (22.6%)	13 (27.1%)	0.642
Symptoms			
Headache	65 (34.9%)	17 (35.4%)	1.000
Visual disturbance	108 (58.1%)	32 (66.7%)	0.358
Polyuria	35 (18.8%)	7 (14.6%)	0.638
Weakness	43 (23.1%)	9 (18.8%)	0.650
Maximal tumor diameter (cm)	2.9 (1.0)	3.2 (0.9)	0.108
Calcification	87 (46.8%)	24 (50.0%)	0.813
No cyst	43 (23.1%)	15 (31.3%)	0.329
Tumor type			
Intrasellar	10 (5.4%)	6 (12.5%)	0.155
Suprasellar	136 (73.1%)	34 (70.8%)	0.893
Third ventricular type	40 (21.5%)	8 (16.7%)	0.488
Puget classification			0.046
Grade 0	46 (24.7%)	18 (37.5%)	
Grade 1	99 (53.2%)	16 (33.3%)	
Grade 2	41 (22.0%)	14 (29.2%)	
Transsphenoidal approach	181 (97.3%)	44 (91.7%)	0.164
Total resection	142 (76.3%)	36 (75.0%)	0.996
Stalk preserved			0.562
No	101 (54.3%)	28 (58.3%)	
Partial	40 (21.5%)	7 (14.6%)	
Complete	45 (24.2%)	13 (27.1%)	
Preoperative lab			
Sodium (mmol/L)	144.4 (5.4)	143.4 (4.1)	0.250
Cortisol (μg/dL)	5.3 (3.2, 10.3)	4.7 (2.5, 7.4)	0.142
Free triiodothyronine (pmol/L)	2.9 (0.7)	2.9 (0.8)	0.970
Free thyroxine (pmol/L)	15.5 (4.6)	15.2 (4.7)	0.716
Outcomes			
Postoperative hypernatremia	101 (54.3%)	24 (50.0%)	0.711
Hypernatremia duration ≥ 3 days	40 (21.5%)	12 (25.0%)	0.746

to preoperative adrenal insufficiency and severe hypernatremia, sex and stalk preservation were also associated with the increased risk.

We first trained seven algorithms in the training cohort. Among all the algorithms trained, the random forest algorithm was the best, compared with the other algorithms, resulting in the highest 5-fold cross-validation AUC (0.770, 95% CI, 0.727–0.813, Table 3, Fig. 2). The sensitivity, specificity, and accuracy of the best model were 66.1%, 43.4%, and 88.4%, respectively. Our models were validated in the validation cohort (prospectively collected data), resulting in an AUC of 0.740. The sensitivity, specificity, and accuracy of the best model were 66.7%, 50.0%, and 83.3%, respectively. The feature importance suggested that preoperative adrenal insufficiency, preoperative severe hypernatremia, and Puget classification were the three most important variables in predicting severe hypernatremia after surgery for craniopharyngioma. Sensitivity analysis excluding patients with preoperative severe hypernatremia yield an AUC of 0.708 in the training cohort and an AUC of 0.689 in the validation cohort.

Among the entire cohort, the proposed model was well calibrated in both the training cohort and validation cohort. Risk stratification allocated 14.0%, 68.3%, and 17.7% of patients to the low-risk, medium-risk, and high-risk groups, respectively. In the low-risk group, 22.7% of patients developed severe hypernatremia. In the medium-risk group, 50.4% of patients developed severe hypernatremia, and in the high-risk group, 90.9% of patients developed severe hypernatremia. Similarly, in the validation cohort, 25% of patients in the low-risk group developed severe hypernatremia, and 100.0% of those in the high-risk group developed severe hypernatremia (Fig. 3).

We simplified the model using these important features to construct a version for clinical use and presented it using a nomogram (Fig. 4). Physicians can add the corresponding scores using the graph and obtain the probability of developing severe hypernatremia.

Table 4 and Figure 5 show that nursing shifts during which patients had a decrease in serum sodium (<4 mmol/L) were associated with higher positive net fluid balance (540 mL), and nursing shifts during which patients had an increase in serum sodium levels (≥4 mmol/L) were associated with lower positive net fluid balance (70 mL). Both oral and intravenous inputs were higher during nursing shifts with a large decrease in serum sodium levels ($P < 0.001$). In contrast, urine output and desmopressin use were similar among the groups. Further analysis comparing day shifts, night shifts, and overnight shifts demonstrated that overnight shifts were associated with the highest serum sodium increase ($P = 0.010$). The possible reasons for this finding include less intravenous input and less desmopressin use ($P < 0.001$).

Discussion

We described the risk pattern of hypernatremia after surgery for craniopharyngioma. Preoperative adrenal insufficiency, preoperative hypernatremia, gross total

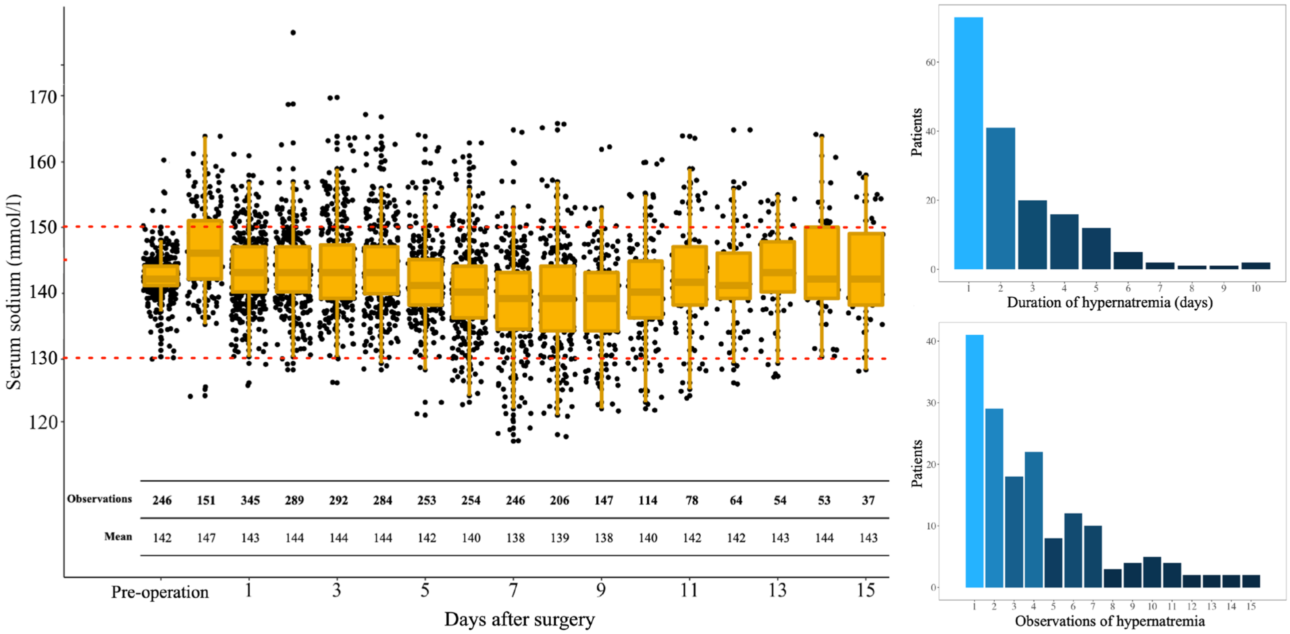

Figure 1
Time distribution of serum sodium levels after surgery for craniopharyngioma. Box represents median and interquartile range.

Table 2 Risk factors associated with postoperative and prolonged postoperative hypernatremia.

	OR	95% CI		*P*
Risk factors associated with postoperative hypernatremia				
Resection extend				0.031
Subtotal	Reference			
Total	2.41	1.10	5.45	
Puget classification				0.026
Grade 0: free of hypothalamus contact	Reference			
Grade 1: hypothalamus contact	2.49	1.13	5.67	
Grade 2: hypothalamus distortion	4.44	1.59	13.22	
Preoperative adrenal insufficiency				0.040
No	Reference			
Yes	2.01	1.04	3.97	
Preoperative hypernatremia				< 0.001
No	Reference			
Yes	5.55	2.71	12.03	
Risk factors associated with prolonged postoperative hypernatremia				
Gender				0.006
Male	Reference			
Female	3.01	1.39	6.75	
Stalk preserved				0.028
Yes	Reference			
No	1.86	1.10	3.37	
Puget classification				0.006
Grade 0: free of hypothalamus contact	Reference			
Grade 1: hypothalamus contact	3.04	1.02	11.39	
Grade 2: hypothalamus distortion	6.27	1.81	26.18	
Preoperative hypernatremia				
No	Reference			0.007
Yes	2.90	1.34	6.41	

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Table 3 Model performance to predict postoperative hypernatremia.

	AUC	Accuracy	Specificity	Sensitivity
Training cohort				
Linear regression	0.659 (0.609–0.709)	60.2% (52.6–67.9%)	37.0% (28.5–45.4%)	81.0% (73.0–89.0%)
LASSO	0.723 (0.677–0.770)	64.5% (62.7–66.3%)	41.8% (37.2–46.4%)	84.5% (81.2–87.8%)
Support vector machine	0.699 (0.625–0.772)	65.6% (56.1–75.0%)	43.8% (35.8–51.8%)	84.9% (79.5–90.2%)
Latent discriminant analysis	0.690 (0.629–0.751)	60.2% (56.5–64.0%)	36.6% (33.3–39.3%)	81.1% (75.0–87.3%)
Random forest	0.770 (0.727–0.813)	66.1% (58.5–75.2%)	43.4% (32.3–48.5%)	88.4% (71.1–93.1%)
Gradient boost model	0.761 (0.676–0.846)	65.7% (59.1–72.1%)	42.4% (35.4–49.4%)	85.2% (82.9–91.2%)
Ensemble model	0.721 (0.651–0.790)	63.4% (58.0–68.7%)	40.1% (34.2–45.9%)	83.2% (78.3–88.1%)
Validation cohort				
	0.740	66.7%	50.0%	83.3%

resection, and high Puget classification were associated with higher risks of developing hypernatremia. We further developed a machine learning model to predict hypernatremia risk. The model uses readily available clinical information as input and outputs the probability as a decision-support tool. Decreased intravenous input and less desmopressin use during the overnight shift were the main reasons for increased serum sodium in postsurgical patients with craniopharyngioma.

The incidence of hypernatremia observed in our cohort was 53.4%, which was comparable with that of a previous study reporting 50% of patients with hypernatremia (4). In that study, age, tumor type, and preoperative arginine vasopressin deficiency were independent prognostic factors for obvious disorders

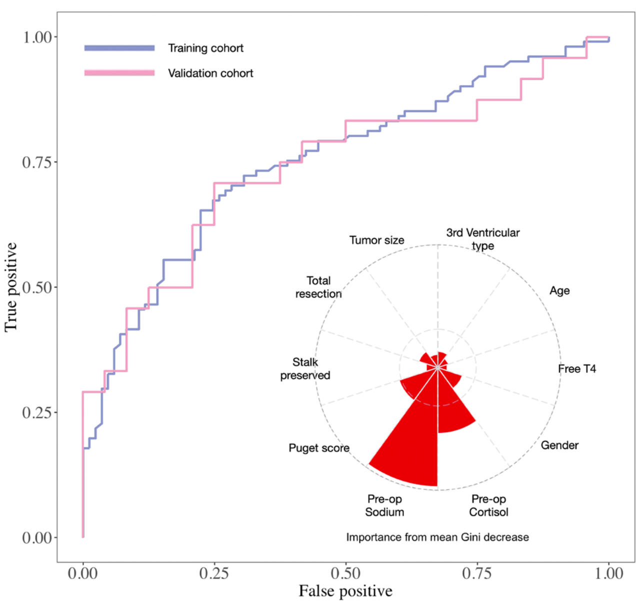

Figure 2
Performance of the proposed model in the training cohort and validation cohort and feature importance (red area).

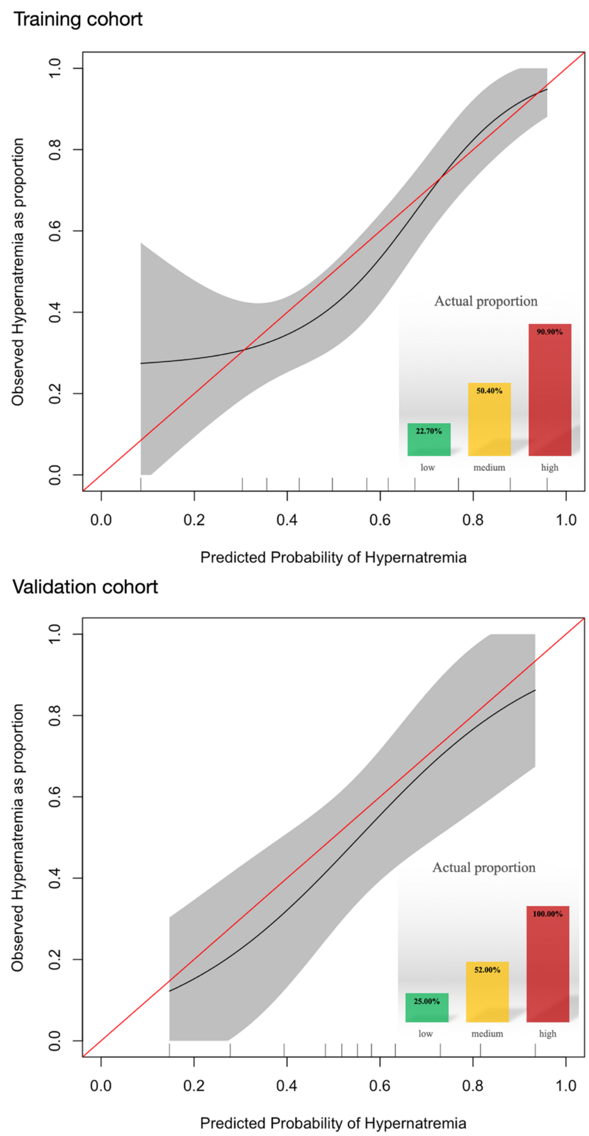

Figure 3
Calibration plot in both the training cohort and validation cohort. Each cohort was further categorized into low, medium, and high risk. The number represents the actual percentage of hypernatremia in that risk category.

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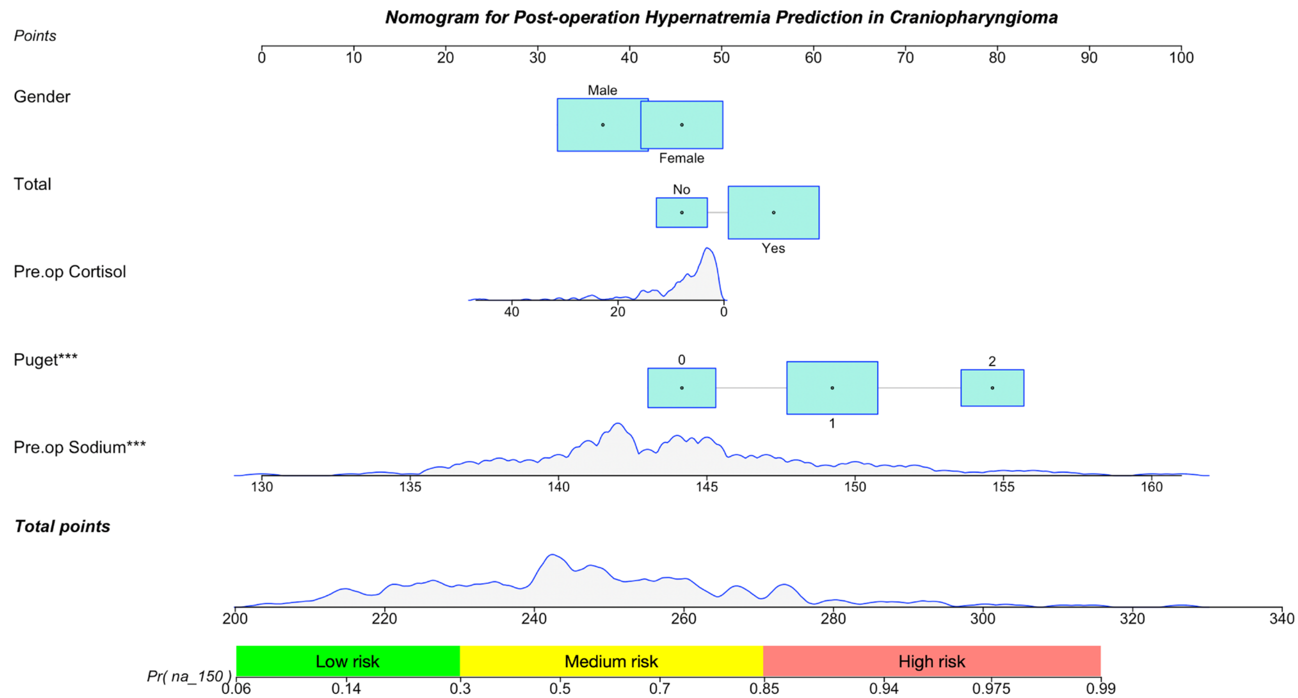

Figure 4
Interactive interface of the nomogram. Users find corresponding points in each feature and add the points to obtain a final point and the corresponding probability of developing hypernatremia.

of serum sodium. We observed a highly increased risk in patients with Puget classification III; these patients had hypothalamus involvement and distortion owing to tumor invasion (7). These patients may require more extensive surgery leading to DI. It was also possible that the masked by hypocortisolism preoperatively became unmasked when getting postoperative steroid.

Compared with conventional statistical assessment of risk factors, machine learning models potentially allow for the inclusion of a broader range of potential risk factors in predictive analysis. In recent years, the increasing availability of electronic health records with easier extraction of patient, diagnostic, and operational factors has yielded a growing amount of data points that can be handled by machine learning models to predict possible outcomes. Previous studies have shown the utility of machine learning techniques to predict various important outcomes in surgeries involving sellar

Table 4 Fluid input and output in different shifts.

	Decrease of Na ≥ 4 mmol/L (*n* = 181)	Decrease of Na < 4 mmol/L (*n* = 1298)	Increase of Na < 4 mmol/L (*n* = 1227)	Increase of Na ≥ 4 mmol/L (*n* = 199)	*P* for different sodium change	Day shifts (*n* = 938)	Night shifts (*n* = 983)	Overnight shifts (*n* = 984)	*P* for different shifts
Sodium difference	−7.6 (4.7)	−1.2 (0.9)	1.1 (1.0)	7.2 (4.0)	<0.001	−0.3 (4.2)	−0.2 (3.0)	0.2 (2.9)	0.010
Intravenous input (mL)	720 (440, 1140)	500 (150, 865)	490 (100, 850)	500 (205, 875)	<0.001	750 (575, 1020)	500 (270, 868)	100 (0, 500)	<0.001
Oral input (mL)	1150 (700, 1710)	924 (600, 1410)	948 (550, 1430)	850 (500, 1300)	<0.001	1000 (700, 1500)	860 (550, 1330)	925 (500, 1500)	<0.001
Total input (mL)	2000 (1510, 2590)	1555 (1052, 2110)	1520 (1000, 2115)	1500 (1014, 1995)	<0.001	1871 (1400, 2329)	1500 (1050, 2021)	1255 (700, 1912)	<0.001
Urine output (mL)	1410 (850, 2160)	1300 (800, 1940)	1300 (800, 1950)	1300 (785, 1960)	0.480	1290 (760, 1948)	1250 (810, 1950)	1355 (830, 1985)	0.134
Fluid balance (mL)	540 (−100, 1120)	170 (−306, 700)	160 (−370, 665)	70 (−422, 586)	<0.001	500 (60, 970)	180 (−300, 634)	−150 (−590, 350)	<0.001
Desmopressin	40 (22.1%)	246 (19.0%)	202 (16.5%)	35 (17.6%)	0.184	285 (30.4%)	115 (11.7%)	123 (12.5%)	<0.001

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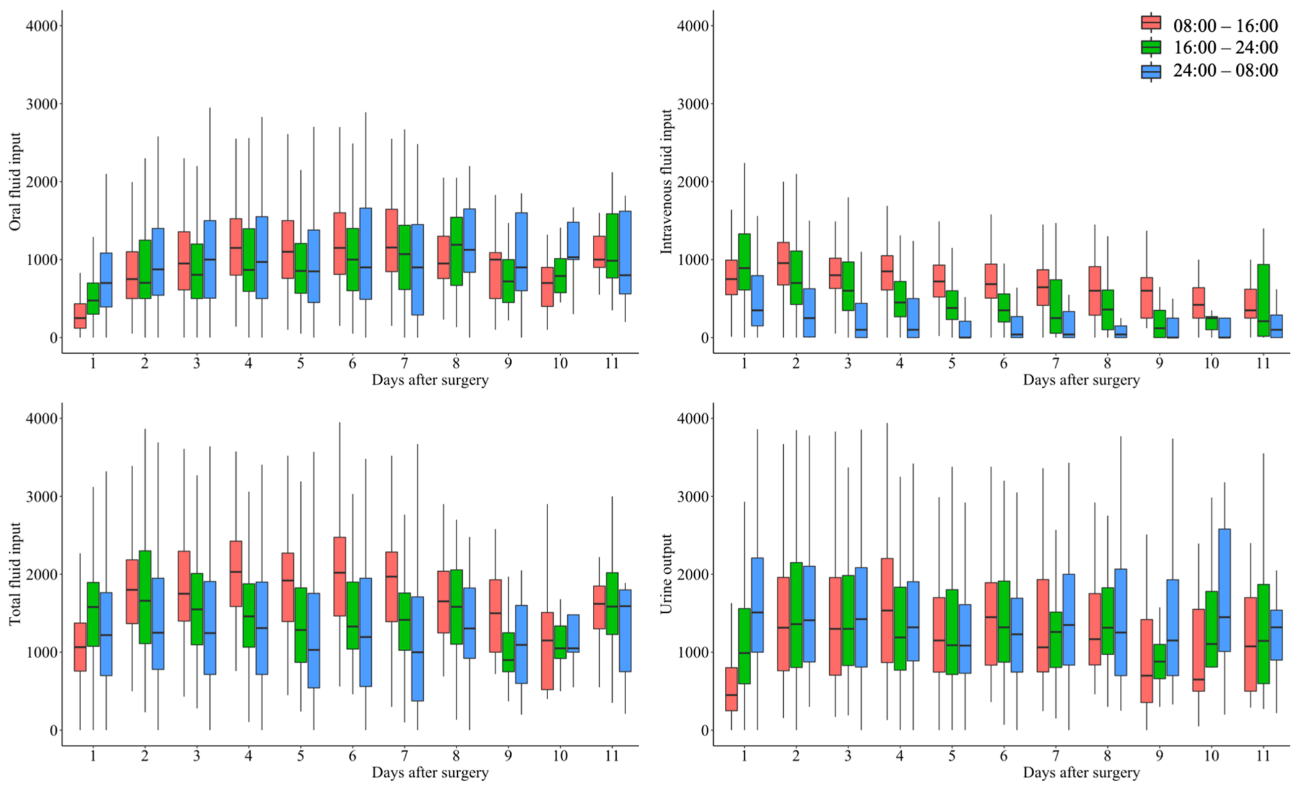

Figure 5
Oral input and intravenous input, total input, and urine output during the postoperative course over three nursing shifts. Box represents median and interquartile range.

region diseases, e.g. visual outcome (8), intraoperative cerebrospinal fluid leaks (9), and hyponatremia (10).

A previous study predicted postoperative arginine vasopressin deficiency after transsphenoidal surgery (11). Improved prediction of arginine vasopressin deficiency could optimize resource allocation and facilitate individualized preoperative patient counseling. The models built in our study had high sensitivity, suggesting very low rates of false-positive results. With use of the models in the clinical setting, patients at high risk can be cared for in an intensive unit under close observation. The postoperative nursing team can initiate preventive procedures to provide sufficient hydration, and patients at low risk can be monitored less frequently.

Patients with craniopharyngioma usually undergo tremendous fluid fluctuation during the first few days after surgery because of arginine vasopressin deficiency. Postoperative arginine vasopressin deficiency is a common complication after pediatric brain tumor surgery in the sellar or suprasellar region. In patients with craniopharyngioma, ongoing renal and extrarenal fluid losses should be considered in the overall fluid prescription. In our study, adults with hypernatremia were often undertreated, especially during overnight shifts.

We also observed an episode of hyponatremia between day 6 and day 9 after surgery. This is possible due to overcorrection of hypernatremia. This triphasic response was also seen in a previous large study of pituitary adenomas (12).

Several limitations exist in this study. First, patients less than 18 years old was excluded. Moreover, the constructed model was not validated using an external database, compromising its clinical generalization. Second, the role of copeptin assays is gaining interest in the diagnosis of water balance disorders (13). A low level of copeptin predicts arginine vasopressin deficiency and thus hypernatremia. However, the availability of copeptin assays and the long turn-around time currently limit the clinical applicability of copeptin. A future study using a new postoperative treatment regimen under the guidance of copeptin to reduce hypernatremia rate might be of interest. Finally, we chose hypernatremia rather than DI as the endpoint, due to the former being easier to identify in a retrospective study.

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Conclusion

In our study, we found that the overall incidence of postoperative severe hypernatremia after surgical resection of craniopharyngioma was high, especially within 5 days after surgery. Patients with hypothalamus involvement, presurgical severe hypernatremia, and adrenal insufficiency had a higher risk of developing postoperative severe hypernatremia. Additionally, reduced intravenous input and less desmopressin use during the overnight shift were the main reasons for serum sodium increase in these patients.

Declaration of interest

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

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Consent for publication

Consent for publication was provided by all authors.

Availability of data and material

The data will be shared upon request after approval of the institution.

Code availability

Code will be shared upon request.

Compliance with ethical standards

This study was approved by the institutional review board of Huashan Hospital and was conducted in accordance with the Declaration of Helsinki. Participants provided informed consent for entering their information into the database.

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