Heliyon 10 (2024) e28958

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Gender potentially affects early postoperative hyponatremia in pituitary adenoma: XGBoost-based predictive modeling

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ARTICLE INFO

Keywords:
Pituitary adenoma
Hyponatremia
Gender
Enhanced recovery after surgery

ABSTRACT

Purpose: The occurrence of hyponatremia is a prevalent complication following transnasal transsphenoidal surgery for pituitary adenoma surgery, which adversely affects patient prognosis, hospitalization duration, and rehospitalization risk. The primary objective of this study is to strengthen the correlation between clinical factors associated with pituitary adenoma and postoperative hyponatremia. Additionally, the study aims to develop a predictive model for postoperative hyponatremia in patients with pituitary adenoma, with the ultimate goal of establishing a basis for reducing the occurrence of postoperative hyponatremia following surgical interventions.

Methods: The chi-square test or Fisher test was employed for nominal data, while the *t*-test or Mann-Whitney test was utilized for continuous data analysis. In cases where the data exhibited statistical differences, binary logistic analysis was conducted to examine the risk and protective factors associated with postoperative hyponatremia. XGBoost was employed to construct predictive models for hyponatremia in this study. The patients were partitioned into training and test sets, and the most suitable parameters were determined through five-fold cross-validation and subsequently utilized for training on the training set. The discriminatory capability was assessed on the internal validation set.

Results and conclusions: Out of the total 280 patients included in this investigation, 82 patients experienced early postoperative hyponatremia. Among these individuals, male gender ($P = 0.02$, odds ratio = 1.98) was identified as a risk factor for early postoperative hyponatremia, while preoperative chloride levels ($P = 0.021$, odds ratio = 0.866) and surgery time ($P = 0.039$, odds ratio = 0.990) were identified as protective factors against postoperative hyponatremia. The XGBoost model exhibited a sensitivity of 94.2%, a specificity of 61.5%, a positive predictive value of 51.6%, a negative predictive value of 96%, and identified male gender, preoperative sodium,

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https://doi.org/10.1016/j.heliyon.2024.e28958
Received 8 December 2023; Received in revised form 26 March 2024; Accepted 27 March 2024
Available online 2 April 2024

and preoperative cortisol as the most significant predictors. Our findings indicate that gender may have influence in the development of early postoperative hyponatremia in patients with pituitary adenomas.

1. Background

Pituitary adenomas constitute 10–15% of intracranial tumors and are the most prevalent sellar lesion [1]. The primary treatment for pituitary adenomas is transnasal sphenoid surgery, which has a low incidence of complications [2]. However, postoperative salt and water imbalance is a common occurrence, with a 28% likelihood of hyponatremia [3]. These electrolyte imbalances can lead to adverse effects such as nausea, vomiting, altered mental status, and seizures, which can prolong hospitalization and increase the risk of readmission [4–7]. Mild electrolyte imbalances may present with non-specific symptoms, such as nausea and vomiting [8], and may go unnoticed. However, if left untreated, electrolyte imbalances can exacerbate and result in various neurological symptoms [9]. Following pituitary adenoma surgery, hyponatremia may occur due to the Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) and Cerebral Salt-Wasting Syndrome (CSWS) [10,11]. While some medical centers administer prophylactic treatment for these conditions, it may lead to the development of compensatory diabetes in patients [5]. Consequently, the recognition of factors that predict electrolyte imbalances is advantageous for the management of pituitary tumor patients after surgery [12].

As hyponatremia plays a crucial role in postoperative recovery, numerous studies have investigated the factors contributing to postoperative hyponatremia in patients with pituitary adenomas. Roxane D Staiger et al. identified patient age, adenoma size, and preoperative pituitary function as potential risk factors for hyponatremia [13]. In contrast, J Hensen et al. proposed that hyponatremia may be more closely associated with the pathological type of pituitary adenoma rather than age, adenoma size, and pituitary growth pattern [14]. David J Cote et al. suggested that advanced age, female gender, macroadenomas, and ACTH adenomas were risk factors for delayed postoperative hyponatremia [15]. Arman Jahangiri posited a potential correlation between hyponatremia and preoperative pituitary hypofunction [16]. Namath S Hussain proposed that factors such as patient age and body mass index could potentially impact the development of hyponatremia, while Gabriel Zada suggested an association between hyponatremia and diabetes insipidus [17,18]. Yusuke Tomita et al. determined that individuals age older than 55 may face an increased risk of postoperative hyponatremia in pituitary adenomas [19]. Despite the extensive research conducted on this topic, there remains a lack of consensus regarding the definitive factors influencing the development of hyponatremia in this patient population. In contrast to prior research that primarily examined delayed postoperative hyponatremia, our current study reveals a significantly higher incidence of early postoperative hyponatremia. Despite the potential for early hyponatremia may go unnoticed, its untreated progression may result in the manifestation of various neurological symptoms [9]. This study aims to conduct a comprehensive analysis of the association between clinical factors of pituitary adenomas and early postoperative hyponatremia, with the ultimate goal of developing a predictive model to guide preventive measures against postoperative hyponatremia.

2. Methods

2.1. Patients

This study is a retrospective analysis conducted at a single center, which included 280 patients diagnosed with pituitary adenoma between October 2020 and October 2022 in local hospital. The inclusion criteria required patients to have not undergone preoperative radiotherapy or chemotherapy, to have undergone preoperative dynamic enhancement of pituitary MRI and cranial CTA resulting in a diagnosis of pituitary adenoma, to have been pathologically diagnosed with pituitary adenoma based on postoperative immunocytology, and the surgical procedure was executed via endoscopy or microscopy through the pterygoid sinus, with exclusion criteria consisting of patients who had undergone traditional craniotomy, had a history of nasopharyngeal surgery or skull base radiation therapy, or presented with skull base fractures, hydrocephalus, or other intracranial occupying lesions. Research involving human subjects were reviewed and approved by hospital research ethics committees. As this study was a retrospective analysis and used non-identified data, informed consent from patients was waived. This study complies with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline [20].

2.2. Data acquisition

In this study, we collected data on patient's gender, age, body mass index (BMI), whether recurrence, disease duration, diabetes mellitus, hypertension, hyperlipidemia, heart disease, hepatic insufficiency, renal insufficiency, hyperuricemia, preoperative sodium, preoperative potassium, preoperative chloride, preoperative urea nitrogen (Bun), preoperative serum creatinine (Cr), preoperative adrenocorticotropic hormone (ACTH), preoperative cortisol, preoperative thyroid stimulating hormone (TSH), preoperative free triiodothyronine (FT3), preoperative free thyroxine (FT4), Preoperative tumor size (anteroposterior, AP), Preoperative tumor size (craniocaudal), Preoperative tumor size (transverse), surgery time, whether total resection, and pituitary stroke. Postoperative blood sodium below 135 mmol/L was diagnosed as hyponatremia.

2.3. Statistics

SPSS 27.0 and Graphpad Prism 8 were used to analyze the data. Normality test and F-test were performed for continuous variables. Data that conformed to normal distribution with equal variances between groups were described using mean ± standard deviation and compared between groups using *t*-test, while data that did not conform to normal distribution were described using M(P25–P75) and compared between components using Mann-Whitney test. For nominal data univariate analysis was performed using chi-square test or Fisher test with a test level of 0.05. For variables with statistical differences, binary logistic regression analysis was used. $P < 0.05$ was considered statistically significant. A predictive model for postoperative hyponatremia following pituitary adenoma surgery was developed utilizing eXtreme Gradient Boosting (XGBoost). The utilization of XGBoost offers the advantage of an additional regularization protocol that effectively mitigates overfitting during the initial model training process [21]. The analysis was conducted employing the XGBoost package in Python version 3.7.9 [22]. A total of 280 patients were divided into a training set (n = 224) and a test set (n = 56). Optimal parameters were determined through a five-fold cross-validation and subsequently utilized for training on the training set. The discriminative ability of the model was assessed on the test set.

3. Results

3.1. The association between postoperative hyponatremia and various clinical factors

Specifically, the study includes data from 82 patients who developed hyponatremia 1 day after surgery. Only 15 patients developed hyponatremia at 7 days postoperatively. In this study we analyzed the relationship between early postoperative hyponatremia and various factors. Nominal data, including gender, recurrence, hypertension, hyperlipidemia, cardiac disease, hepatic insufficiency, renal insufficiency, hyperuricemia, mode of resection, and pituitary stroke, were analyzed using the chi-square test. Continuous variables were compared between groups using the *t*-test and Mann-Whitney test. Tables 1 and 2 demonstrate notable variances in the incidence of postoperative hyponatremia concerning gender, disease duration, preoperative sodium, preoperative potassium, preoperative chloride, and surgical time. A multifactorial logistic regression was performed, encompassing 6 factors, revealing that male gender was a risk factor for postoperative hyponatremia, while preoperative chloride and surgery time were protective factors (Table 3).

Table 1
Univariate analysis of the association between postoperative hyponatremia and nominal data.

	Non-hyponatremia(n = 198)		Hyponatremia(n = 82)		χ^2	*P*
	Number	Percentage(%)	Number	Percentage(%)		
Gender					9.168	0.0025
Male	95	48.48	56	68.29		
Female	103	51.52	26	31.71		
Onset of disease					0.4959	0.4813
Recurrence	17	8.59	5	6.1		
First episode	181	91.41	77	93.9		
Diabetes					1.958	0.1617
Yes	49	24.75	14	17.07		
No	149	75.25	68	82.93		
Hypertension					0.1187	0.7304
Yes	67	33.84	26	31.71		
No	131	66.16	56	68.29		
Hyperlipidemia					0.001018	0.9746
Yes	97	48.99	40	48.78		
No	101	51.01	42	51.22		
Heart disease					0.007665	0.9302
Yes	20	10.1	8	9.76		
No	178	89.9	74	90.24		
Liver function					0.2038	0.6516
Abnormal	25	12.63	12	14.63		
Normal	173	87.37	70	85.37		
Kidney function					0.3703	0.5428
Abnormal	19	9.6	6	7.32		
Normal	179	90.4	76	92.68		
Hyperuricemia					1.051	0.3052
Yes	31	15.66	17	20.73		
No	167	84.34	65	79.27		
Excision method					2.327	0.1271
Total excision	121	61.11	58	70.73		
Incomplete resection	77	38.89	24	29.27		
Pituitary stroke					0.5662	0.4518
Yes	38	19.19	19	23.17		
No	160	80.81	63	76.83		

Table 2
Univariate analysis of the association between postoperative hyponatremia and continuity data.

	Non-hyponatremia(n = 198)	Hyponatremia(n = 82)	t	U	*P*
Age	53.00 (42.75–60.00)	50.98 ± 14.26		7763	0.5656
BMI	24.36 (22.73–27.11)	24.39 (22.31–26.81)		7759	0.5608
Disease duration (year)	0.6 (0.1–3.0)	0.35 (0.1–1.0)		6747	0.024
Preoperative sodium	141.0 (139.8–142.3)	139.4 ± 2.347		4892	< 0.0001
Preoperative potassium	3.980 (3.798–4.213)	4.077 ± 0.3147		6799	0.0323
Preoperative chloride	105.3 ± 2.577	104.3 ± 2.506	3.003		0.0029
Preoperative Bun	5.000 (4.075–5.700)	4.947 ± 1.305		7769	0.5722
Preoperative Cr	59.00 (49.75–70.25)	63.00(52.75–71.00)		7567	0.3719
Preoperative ACTH	5.435 (3.683–8.485)	5.395 (4.033–8.420)		7926	0.7557
Preoperative cortisol	334.2 (194.3–509.7)	337.8 ± 203.0		7770	0.5735
Preoperative TSH	1.635 (0.895–2.355)	1.545 (1.018–2.473)		8047	0.9082
Preoperative FT3	4.040 (3.595–4.713)	4.407 ± 1.167		7022	0.0755
Preoperative FT4	14.30 (11.30–16.30)	14.20 (11.98–16.10)		7934	0.7655
Preoperative tumor size(AP)	2.1 (1.7–2.7)	2.0 (1.7–2.5)		7622	0.4210
Preoperative tumor size(craniocaudal)	1.8 (1.5–2.2)	1.7 (1.4–2.1)		7748	0.5482
Preoperative tumor size(transverse)	1.800 (1.275–2.300)	1.95 (1.40–2.20)		7845	0.6581
Surgery time	105 (90.0–125.0)	100 (80.0–116.3)		6639	0.0160

Table 3
Binary logistic regression analysis of postoperative hyponatremia.

Factors	B	S.E.	Wald	*P*	OR	95% CI	
						Lower limit	Upper limit
Male	0.683	0.293	5.418	0.02	1.98	1.114	3.519
Disease duration	−0.082	0.047	2.993	0.084	0.922	0.84	1.011
Preoperative sodium	−0.056	0.048	1.349	0.245	0.946	0.861	1.039
Preoperative potassium	0.541	0.416	1.688	0.194	1.718	0.759	3.885
Preoperative chloride	−0.143	0.062	5.347	0.021	0.866	0.767	0.978
Surgery time	−0.010	0.005	4.253	0.039	0.990	0.981	1.000

3.2. Predictive performance of XGBoost model

Fig. 1 presents a summary of the prediction performance of the XGBoost algorithm in the test cohort, with an area under the curve (AUC) value of 0.86. Additionally, Fig. 2 demonstrates the favorable precision-recall performance of the XGBoost model, indicated by an average precision (AP) value of 0.74. The decision thresholds for the XGBoost model were optimized using the Youden index. At this optimized threshold, the XGBoost model exhibited a sensitivity of 94.2%, a specificity of 61.5%, a positive predictive value of 51.6%, and a negative predictive value of 96%.

3.3. Variable importance

Fig. 3 illustrates the order of importance of the variables in the XGBoost model, with male gender, preoperative sodium, and preoperative cortisol being the top three influential factors.

4. Discussion

Over the course of a century, transsphenoidal surgery, initially introduced by Schloffer in 1907, has evolved into the preferred treatment modality for pituitary adenomas [23]. The transsphenoidal approach for pituitary adenoma surgery represents a significant progression in minimally invasive surgical techniques. In contrast to conventional craniotomy surgery, transsphenoidal surgery is distinguished by reduced tissue damage, decreased operative duration, and expedited postoperative recuperation. While transsphenoidal surgery is considered a safer alternative, electrolyte imbalances, particularly hyponatremia and hypokalemia, are frequently encountered [24,25].

The regulation of blood sodium levels is primarily governed by the hypothalamic-pituitary-vasopressin system and the renin-angiotensin-aldosterone system (RAAS). The hypothalamus is responsible for the production of vasopressin hormone (ADH), which facilitates the repeated absorption of water by the renal tubular epithelium. In cases where the extracellular fluid and effective blood volume of the body are inadequate, sympathetic excitation and increased secretion of hormones from the adrenal medulla activate the RAAS, which regulates water-sodium balance. Hyponatremia, a condition characterized by low sodium levels, can be attributed to SIADH and CSWS following pituitary adenoma. During surgical intervention for pituitary adenomas, the hypothalamus may be directly or indirectly impacted, leading to the release of significant quantities of antidiuretic hormone (ADH) from the posterior pituitary and consequent increased water reabsorption by the renal tubules, resulting in water retention and the onset of hyponatremia [26]. The

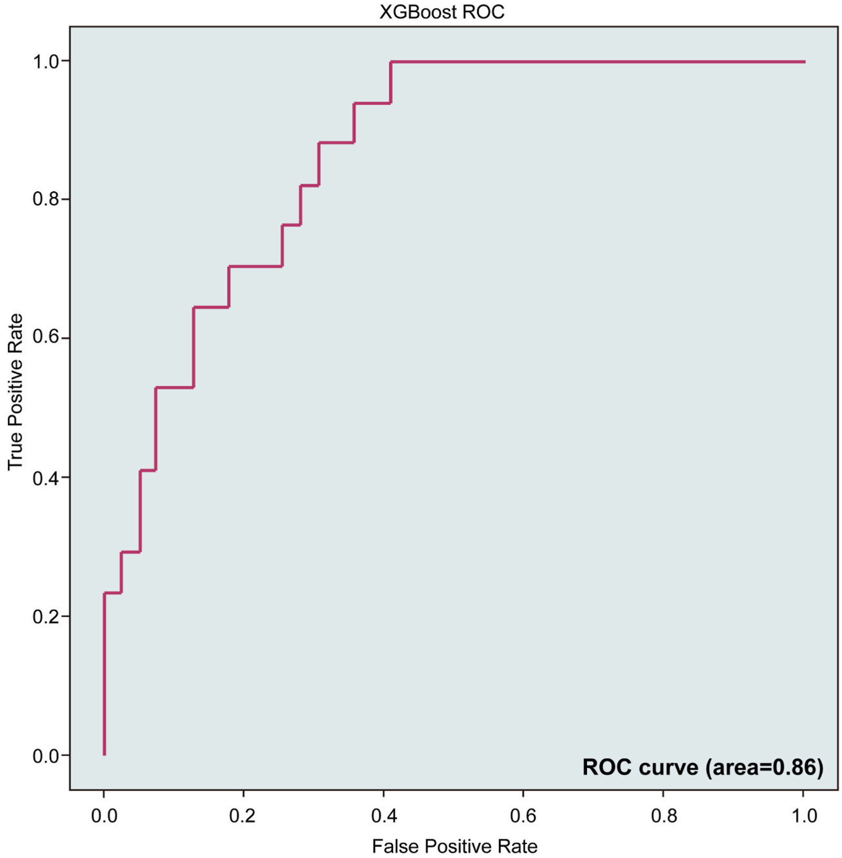

Fig. 1. Area under the receiver operating characteristic curves showed the predictive ability of XGBoost model.

occurrence of CSWS may be attributed to elevated levels of circulating natriuretic peptides, reduced sympathetic stimulation of the kidneys, and decreased levels of renin and aldosterone, which diminish sodium retention [10]. In addition to hyponatremia, CSWS may also present with hypovolemia. Consequently, the clinical management of SIADH and CSWS differs significantly.

In recent years, there has been a growing focus on enhanced recovery after surgery (ERAS). ERAS is a perioperative approach that seeks to minimize surgical stress and postoperative complications by implementing evidence-based measures. This approach offers several benefits, including a reduction in hospital stay duration, decreased hospitalization costs, expedited patient recovery, and the assurance of maintaining surgical efficacy and patient safety [27]. Previous studies have predominantly examined delayed hyponatremia occurring after 3 days postoperatively in patients with pituitary adenomas [28]. In contrast, our findings indicate that early postoperative hyponatremia has a significantly higher probability of occurrence, approximately 29.3%, compared to delayed hyponatremia. This suggests that perioperative electrolyte imbalances are more prevalent in patients with pituitary adenomas. Consequently, it is crucial to identify the factors influencing early postoperative hyponatremia and implement early interventions to facilitate enhanced recovery following surgery.

The maintenance of electrolyte, acid-base, and osmolality equilibrium within the body necessitates the significance of blood sodium, blood chloride, and blood potassium. The discernible dissimilarities observed in preoperative blood sodium, potassium, and chloride levels between individuals with hyponatremia and those without hyponatremia indicate that preoperative electrolyte imbalances may contribute to the development of postoperative hyponatremia. Furthermore, it was observed that non-hyponatremia patients exhibited a prolonged period of morbidity and surgery compared to their hyponatremia counterparts. The extended duration of illness in non-hyponatremia patients may be attributed to the impact of onset time on the patient's capacity to make compensatory electrolyte adaptations. While our findings imply that the surgery time serves as a protective factor against postoperative hyponatremia, the inclusion of multicenter studies is imperative to elucidate the precise influence of surgery duration on the occurrence of hyponatremia.

Prophylaxis treatment serves as a therapeutic approach aimed at preventing the occurrence of postoperative hyponatremia in individuals with pituitary tumors. However, the effectiveness of this modality is hindered by the absence of accurate prediction methods. Consequently, it is imperative to develop predictive models that can discern the specific patients who necessitate prophylactic treatment. In this particular investigation, we employed the XGBoost model to construct a predictive model for postoperative hyponatremia in individuals with pituitary adenomas. The XGBoost algorithm, a machine learning technique rooted in gradient boosting trees, offers several advantages over traditional gradient boosting algorithms in disease prediction [21]. Specifically, XGBoost

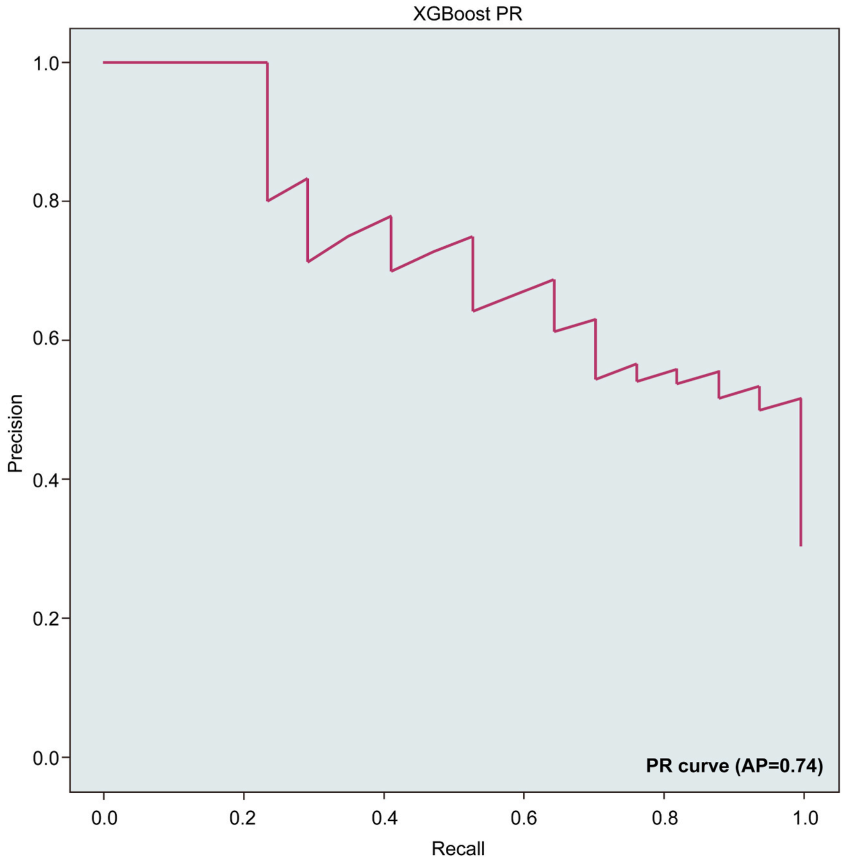

Fig. 2. Precision recall curves for XGBoost model are shown with associated area under the curve.

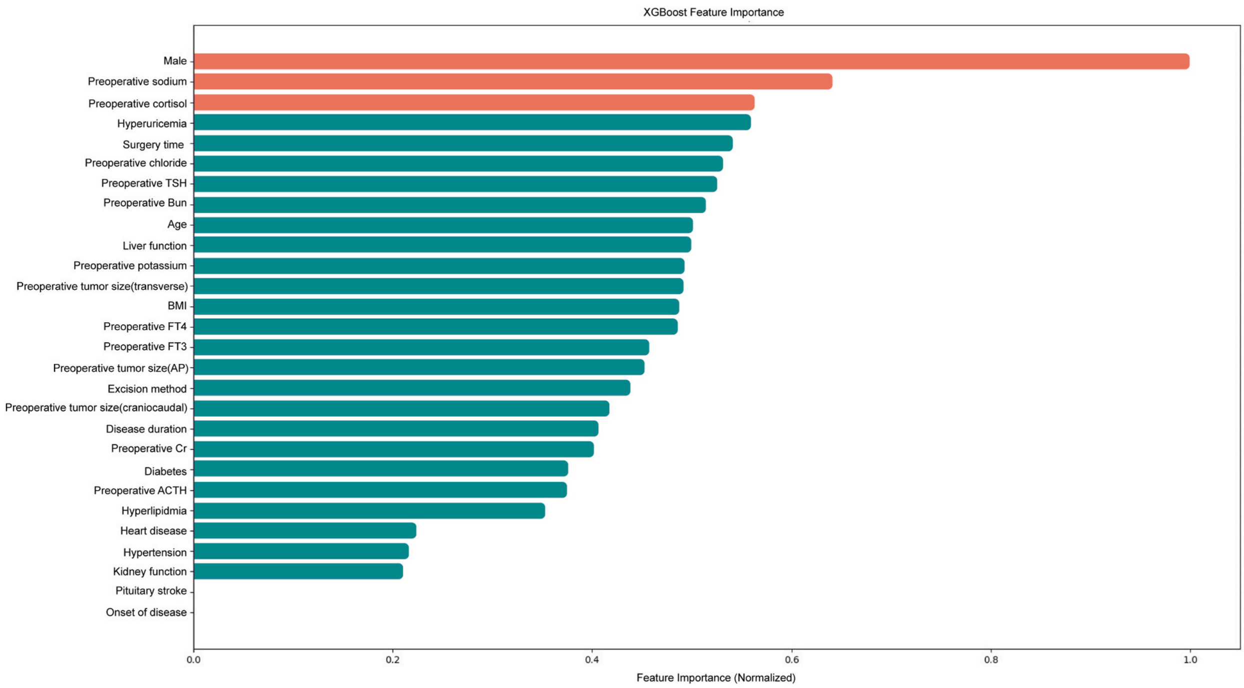

Fig. 3. Relative feature importance of the XGBoost model developed.

demonstrates strong performance with large-scale datasets, efficient parallel processing capabilities, iterative model optimization, superior prediction accuracy compared to other algorithms, and the ability to provide feature importance assessments for enhanced understanding of the prediction process [21,29]. The XGBoost model exhibited a sensitivity of 94.2%, a specificity of 61.5%, a positive predictive value of 51.6%, a negative predictive value of 96%, which suggested a good predictive performance for hyponatremia. When using a predictive model, the data needs to be set to a pattern recognizable by the procedure, and early postoperative hyponatremia can subsequently be predicted based on the patient's preoperative condition. Notably, the most influential factors in this model were male gender, preoperative sodium levels, and preoperative cortisol levels. Remarkably, male gender emerged as the most significant determinant within the predictive model. Prior research has similarly documented the influence of gender as a risk factor in the development of postoperative hyponatremia in individuals with pituitary tumor adenomas [30–32]. In this trial, a total of 280 patients were examined, and a notable disparity in the occurrence of hyponatremia was observed between genders. Our findings indicate that males are more susceptible to early postoperative hyponatremia, contradicting previous literature suggesting that females may be at a higher risk for delayed hyponatremia [31–34]. This discrepancy could potentially be attributed to variations in basal metabolic rate between men and women [35,36], as well as potentially higher nutritional intake among males [37]. There are potential variations in dietary patterns and behaviors between males and females [38]. Influenced by physiological and psychosocial factors, women tend to restrain eat and diet compared to men [39,40], potentially indicating a higher tolerance for hunger and regulation. Furthermore, females commonly adhere to a low-salt diet [38]. However, preoperative fasting may lead to reduced sodium intake [41], which could result in men being less tolerant of this dietary restriction. Additionally, women typically possess a higher percentage of body fat than men [42], potentially enabling them to better compensate for short-term metabolic disruptions caused by preoperative fasting. Consequently, men may experience difficulties in tolerating the consequences of preoperative fasting. In future investigations, we aim to elucidate the impact of preoperative fasting on postoperative perioperative electrolyte levels in both male and female individuals. In fact, the present description is still conjectural. There exist disparities between males and females in relation to basal metabolic rate, dietary patterns, and psychosocial habits [35–38]; however, the extent to which these factors contribute to gender disparities in early postoperative hyponatremia necessitates further investigation. While we have identified this clinical phenomenon, the precise etiology remains to be comprehensively examined. In our subsequent endeavors, we aspire to augment the sample size and conduct a multicenter study to elucidate the impact of males on early postoperative hyponatremia. Additionally, we aim to employ animal experimentation as a means to further explore the mechanisms involved. The predictive significance of preoperative sodium levels in the occurrence of postoperative hyponatremia is easily comprehensible. Furthermore, it is plausible that this effect may persist after surgery, particularly in cases of preoperative electrolyte imbalances, specifically disturbances in sodium metabolism. This implies that early intervention is necessary for preoperative hyponatremia. Cortisol plays a crucial role in the regulation of sodium metabolism, with low cortisol levels resulting in increased urinary sodium excretion and decreased potassium excretion, ultimately leading to hypokalemia. The XGBoost model indicates the importance of closely monitoring preoperative fluctuations in cortisol levels.

Our research findings indicate that gender may have a significant influence on the outcome under investigation. However, it is important to acknowledge that the small sample size utilized in this study may not provide sufficient evidence to establish a definitive conclusion. Consequently, the limited sample size represents a constraint in this study. To address this limitation, future investigations should aim to expand the sample size and employ a multi-center clinical study design to comprehensively examine the impact of gender on early postoperative hyponatremia. When the sample size is further expanded, we will also analyze the risk factors and develop a predictive model for delayed hyponatremia. Additionally, it is worth noting that previous studies have identified other factors, such as the subtype of pituitary adenoma and age, as potential contributors to delayed hyponatremia [13,30]. The surgical context is an additional variable that warrants consideration. When a patient undergoes resection or manipulation of the pituitary stalk, the likelihood of developing diabetes insipidus rises, consequently elevating the risk of hyponatremia. In our forthcoming investigation, we aspire to incorporate these factors into the evaluation of early postoperative hyponatremia, thereby enabling a more comprehensive appraisal of this condition. In clinical practice, certain instances of hyponatremia may not exhibit apparent clinical manifestations, while others may result in the development of clinical symptoms. Our forthcoming study endeavors to discern the hyponatremia cases that affect ERAS and to prognosticate and appraise them.

5. Conclusions

In this study, a total of 280 patients were included, out of which 82 patients developed early postoperative hyponatremia. Among these individuals, male gender ($P = 0.02$, odds ratio = 1.98) was identified as a risk factor for early postoperative hyponatremia, while preoperative chloride levels ($P = 0.021$, odds ratio = 0.866) and surgery time ($P = 0.039$, odds ratio = 990) were identified as protective factors against postoperative hyponatremia. Our research endeavors to establish a prognostic model for perioperative hyponatremia in pituitary adenomas, with the intention of offering valuable insights for the ERAS protocol specific to pituitary adenoma cases. The XGBoost model exhibited a sensitivity of 94.2%, a specificity of 61.5%, a positive predictive value of 51.6%, a negative predictive value of 96%, and identified male gender, preoperative sodium, and preoperative cortisol as the most significant predictors. These findings suggest that gender may play a role in influencing the occurrence of early postoperative hyponatremia in patients with pituitary adenomas. In the realm of clinical practice, it is imperative to prioritize the monitoring of electrolyte levels during the initial postoperative phase in male patients afflicted with pituitary adenomas. This measure is crucial in averting and appropriately rectifying hyponatremia, ultimately leading to ERAS of patients. Furthermore, it is recommended to closely monitor preoperative sodium levels and preoperative cortisol levels.

Funding

This work was supported by Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China (2022-LCYJ-MS-34 for Zong Zhuang, 2022-LCYJ-PY-38 for Wei Li, and 2022-LCYJ-MS-37 for Chun-Hua Hang).

Consent for publication

Not applicable.

Data availability statement

Data associated with this study has not been deposited into a publicly available repository. The datasets and materials are available from the corresponding authors on reasonable request.

Ethics declarations

Research involving human subjects were reviewed and approved by research ethics committees of Drum Tower Hospital (No. 20180323). Informed consent was not required for this study because this study was a retrospective analysis and used non-identified data.

CRediT authorship contribution statement

Zheng Peng: Writing – original draft. **Xiao-Jian Li:** Conceptualization. **Yun-feng Wang:** Data curation. **Zhuo-Yuan Li:** Formal analysis. **Jie Wang:** Funding acquisition. **Chun-Lei Chen:** Investigation. **Hui-Ying Yan:** Methodology. **Wei Jin:** Project administration. **Yue Lu:** Resources. **Zong Zhuang:** Software. **Chun-Hua Hang:** Supervision. **Wei Li:** Validation.

Declaration of competing interest

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

Acknowledgements

Not applicable.

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