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Original Article

Construction of risk predictive models for postoperative hyponatremia in colorectal cancer patients

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Abstract: This study aimed to construct and validate a risk prediction model for postoperative hyponatremia in patients with colorectal cancer (CRC). Clinical data from 280 CRC patients hospitalized at WUZHOU RED CROSS HOSPITAL between January 2021 and December 2024 were retrospectively collected. Patients were categorized into a hyponatremia group and a normal serum sodium group according to postoperative serum sodium levels. All eligible participants were randomly allocated into a training set (70%) and an internal validation set (30%) using R software, while an additional 47 prospectively enrolled CRC patients between January and May 2025 were included as the external validation set. Independent risk factors for postoperative hyponatremia were screened, and four prediction models, including a nomogram, random forest, decision tree, and back-propagation (BP) neural network, were established and comparatively evaluated. Among the 280 enrolled patients, the overall incidence of postoperative hyponatremia was 30.71%. Significant differences were observed between the two groups in syndrome of inappropriate antidiuretic hormone secretion (SIADH) status, TNM stage, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr), carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA) were observed between the two groups (all $P<0.05$). Multivariate logistic regression identified SIADH, advanced TNM stage, elevated Cr, CA19-9 and CEA levels as independent risk factors for postoperative hyponatremia. Comparative evaluation revealed that the random forest model achieved the best predictive performance. The AUC, sensitivity and specificity were 0.985 (95% CI: 0.972-0.997), 96.6% and 92.0% in the training set, respectively; and the corresponding values were 0.845 (95% CI: 0.750-0.940), 82.1% and 83.9% in the internal validation set, respectively. The prospective external validation set further confirmed the superior predictive accuracy of the random forest model. In conclusion, the random forest-based model established in this study demonstrated favorable discrimination and generalization ability for predicting postoperative hyponatremia in CRC patients, thereby providing a useful tool for preoperative risk stratification and early targeted clinical intervention.

Keywords: Colorectal cancer, hyponatremia, nomogram, random forest, decision tree, BP neural network, risk prediction

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, with substantial morbidity and mortality [1]. In China, the incidence of CRC has shown a continuous upward trend, especially among individuals over 50 years, and its morbidity and mortality rates rank among the highest of all cancers. The development and progression of CRC are affected by many factors, including genetic susceptibility and environmental exposures. Despite advances in diagnosis and treatment, a considerable proportion of patients still die from complications, local recurrence, or distant metastasis [2].

Hyponatremia is a common complication in CRC patients and is primarily characterized by decreased serum sodium concentration resulting from disturbances in water and electrolyte homeostasis [3]. Serum sodium plays a critical role in maintaining electrolyte and osmotic balance in the body [4]. Hyponatremia may impair electrophysiological function and adversely affect the efficacy of radiotherapy and chemo-

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therapy in patients with malignant tumors, resulting in poor clinical outcomes. Choi et al. [5] reported that a substantial proportion of hospitalized patients developed hyponatremia, and even mild hyponatremia was associated with increased long-term mortality risk. Therefore, hyponatremia should be considered an important prognostic factor in CRC, and prevention of hyponatremia may contribute to improved prognosis [6]. Early identification and intervention for patients at high risk of hyponatremia are of great significance for optimizing treatment efficacy and improving prognosis.

With the rapid development of the era of big data, machine learning techniques have demonstrated good performance in early disease screening, risk assessment, and prognosis prediction [7-9]. A Nomogram is a graphical predictive tool commonly developed based on regression models and is widely used for disease risk prediction and survival analysis to assist clinicians in individualized decision-making [10]. Random forest is an ensemble learning algorithm composed of multiple decision trees, characterized by high predictive accuracy and strong capability in handling high-dimensional data and complex nonlinear relationships [11]. Decision tree models possess a tree-like structure that facilitates interpretation and clearly shows the decision-making process [12]. The back-propagation (BP) neural network is a multi-layer feedforward neural network trained using back-propagation algorithm and exhibits strong nonlinear mapping ability, making it suitable for solving complex nonlinear relationships [13].

To date, few studies have focused on risk prediction models for postoperative hyponatremia in CRC patients. Therefore, this study retrospectively collected clinical information from 280 CRC patients and aimed to construct four predictive models based on machine learning algorithms, including a nomogram, random forest, decision tree, and BP neural network, in order to establish a more accurate and effective tool for predicting the risk of hyponatremia in CRC patients.

Objects and methods

Study population

This retrospective study enrolled 280 patients with CRC who were admitted to Wuzhou Red Cross Hospital between January 2021 and December 2024. This study was approved by the Ethics Committee of Wuzhou Red Cross Hospital. All procedures were performed in accordance with the Helsinki Declaration (1964) and its subsequent amendments.

Inclusion criteria: (1) Patients were newly diagnosed with CRC [14]; (2) Patients underwent radical resection of CRC at our hospital, and postoperative pathological examination confirmed primary colorectal malignant tumor; and (3) Patients received standardized postoperative guidance on fluid and dietary intake provided by the nutrition team.

Exclusion criteria: (1) Patients with other malignant tumors, severe hepatic or renal dysfunction, or abnormal adrenal and thyroid function; (2) Patients with consumptive diseases associated with hyponatremia, including tumor-associated cachexia (defined as weight loss >5% with BMI <18.5 kg/m^2 or albumin <30 g/L), chronic infections such as active tuberculosis, HIV infection, or fungal sepsis, and severe hepatic dysfunction or renal failure; (3) Patients with transient hyponatremia caused by insufficient sodium intake. Transient hyponatremia was defined as a postoperative serum sodium levels <135 mmol/L at any time point that spontaneously recovered to ≥135 mmol/L within 72 hours without hypertonic saline intervention; and (4) Patients using diuretics or proton pump inhibitors.

Sample size calculation

Sample size estimation was performed according to the principle of at least 10 events per predictor variable (EPV) [15]. Initially, 8 predictive variables were planned for inclusion, with an expected positive event rate of 30%. Thus, the required number of positive events was calculated as E = 10×8 = 80, resulting in a minimum required sample size of n = 80/0.30 = 267 cases. After univariate and multivariate regression screening, 5 independent predictive variables were finally incorporated into the final model. A total of 280 patients, including 86 positive events, were eventually enrolled, which satisfied the recommended 10 EPV criterion and supported the stability and reliability of the predictive model.

Methods

Patient information collection: Medical records were independently reviewed and extracted from the hospital's surgical information system by two investigators. Based on clinical experience and literature review, 26 variables potentially associated with postoperative hyponatremia in CRC patients were included in the analysis.

The collected general information included gender, age, comorbidities (hypertension, diabetes mellitus), syndrome of inappropriate antidiuretic hormone secretion (SIADH), tumor differentiation, TNM stage, adjuvant radiotherapy, adjuvant chemotherapy, and surgical approach. Laboratory parameters obtained at admission included white blood cell (WBC), platelet count (PLT), hemoglobin (Hb), fibrinogen (Fib), total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), cystatin C, creatinine (Cr), urea nitrogen, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), serum potassium, serum calcium, and serum sodium levels.

SIADH diagnostic criteria: (1) Serum sodium <130 mmol/L; (2) Plasma osmolality <270 mOsm/L; (3) Inappropriately elevated urine osmolality, defined as urine osmolality remaining higher than plasma osmolality despite decreased plasma osmolality; (4) Increased urinary sodium excretion (>20 mmol/L); and (5) Normal thyroid, liver, kidney, heart and adrenal cortex function. A diagnosis of SIADH can be made when at least two of the above criteria were satisfied.

Grouping: The diagnostic criteria for hyponatremia [16]: the reference range for serum sodium was 135-145 mmol/L. Mild hyponatremia was defined as serum sodium level of 130-134 mmol/L; moderate hyponatremia was defined as serum sodium level of 120-129 mmol/L; and severe hyponatremia was defined as serum sodium level <120 mmol/L. Serum sodium level was measured daily after surgery.

In this study, patients with serum sodium level <135 mmol/L after radical resection of CRC were included in the hyponatremia group (Hyp group, n = 86), and those with serum sodium level ≥135 mmol/L were included in the normal serum sodium group (NBS group, n = 194). Follow-up observation was continued until hospital discharge.

Construction of the training and validation sets: A total of 280 CRC patients were randomly divided into two datasets at a ratio of 7:3 using the "sample" function in R software, with a random seed number set to 1234. The training set (n = 196) consisted of 60 patients in the Hyp group and 136 in the NBS group, whereas the internal validation set (n = 84) included 28 and 56 in the Hyp and NBS groups, respectively. In addition, 47 consecutive CRC patients admitted between January and May 2025 were prospectively enrolled as the external testing set. The inclusion and exclusion criteria were identical to those described above.

Statistical method

The proportion of missing data for all enrolled variables was summarized. No variable exhibited a missing rate exceeding 10%. Variables with missing values below 10% were imputed using the random forest imputation algorithm with default parameters in *R* software. Variables with a missing rate >10% was excluded in advance to minimize potential selection bias.

SPSS 29.0 and R software (version 4.4.3) were used for data analyses. The Shapiro-Wilk test was used to assess the normality of measurement data. Normally distributed data were presented as mean ± standard deviation and compared using the independent-samples t-test, whereas non-normally distributed variables were analyzed using nonparametric tests. Categorical variables were presented in percentages and compared using chi-square tests. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with postoperative hyponatremia in CRC patients. Variance inflation factor (VIF) analysis was performed to evaluate multicollinearity among predictors included in the multivariate logistic regression model. All VIF values were <5 and tolerance values were >0.20, confirming absence of obvious multicollinearity. A two-sided *P* value <0.05 was considered statistically significant.

Based on the identified independent risk factors, four predictive models were established, including a nomogram model, random forest model, decision tree model, and BP neural network model.

(1) Nomogram model: A logistic nomogram visualization risk model was constructed using the *rms* package in R.

(2) Random-forest model: The random-forest classification model was constructed using the *randomForest* package in R. The number of decision trees was set to 500, and the number of candidate variables randomly selected at each split was defined as the square root of the total number of predictor variables.

(3) Decision tree model: The decision tree model was established using the *rpart* package in R, with the Gini coefficient minimization criterion applied for feature selection and node splitting.

(4) BP neural network model was constructed using the *neuralnet* package in R. A classic three-layer topological structure (input layer, hidden layer, output layer) was adopted. The input layer contained five nodes corresponding to the selected feature variables, whereas the output layer consisted of one node representing the presence or absence of postoperative hyponatremia. The optimal hidden-layer structure was determined using 5-fold cross-validation. Single hidden-layer configurations containing 1-15 neurons were tested, and finally, a configuration with 10 neurons was selected based on the minimum mean squared error (MSE) observed in the validation set. The Sigmoid activation function (*act.fct* = "logistic") was applied in the hidden layer, while linear activation was used in the output layer. The resilient backpropagation algorithm (*RPROP+, algorithm* = "rprop+") was adopted to adaptively adjusts the weight update step size without manual specification of the learning rate. The sum of squared errors (SSE) was used as the loss function, the convergence threshold was set at 0.01, and the maximum number of iterations was 1,000,000. To reduce overfitting, L2 regularization and early stopping combined with 5-fold cross-validation were further applied to optimize network structure and enhance model generalization performance.

The output variable was defined as the presence of postoperative hyponatremia in CRC patients. Model performance was evaluated using receiver operating characteristic (ROC) curves, area under the ROC curve (AUC), sensitivity, specificity, and accuracy.

Results

Clinical data analysis

Among the 280 patients with CRC included in this study, 86 developed hyponatremia, with an incidence of 30.71%.

Compared with the NBS group, patients in Hyp group exhibited significantly higher rates of SIADH and advanced TNM stage (III-IV), as well as significantly elevated levels of Cr, CA19-9, and CEA (all $P<0.05$). No significant differences were observed between the two groups in terms of sex, age, hypertension, diabetes, tumor differentiation, adjuvant radiotherapy/chemotherapy, surgical approach, WBC, PLT, Hb, Fib, TBIL, AST, ALT, cystatin C, urea nitrogen, HDL-C, LDL-C, serum potassium, or serum calcium (all $P>0.05$) (**Table 1**).

Multivariate logistic regression analysis

The occurrence of postoperative hyponatremia in CRC patients (Yes = 0, No = 1) was defined as the dependent variable, while variables with statistical significance in the univariate analysis were included as independent variables. Categorical variables were coded as follows: SIADH (Yes = 0, No = 1) and TNM stage (III~IV = 1, I~II = 0). Continuous variables, including Cr, CA19-9, and CEA were included in the regression model as original continuous values. Multicollinearity analysis showed that the all predictors had VIF <5 and tolerance values >0.20, indicating no significant multicollinearity among the included variables. Specifically, the VIF values were 1.26 for SIADH, 1.33 for TNM stage, 1.41 for Cr, 1.18 for CA19-9, and 1.35 for CEA, with an overall range of 1.18-1.41. Thus, all predictors were retained in the multivariate logistic regression model.

As shown in **Table 2** and **Figure 1**, SIADH, advanced TNM stage (III~IV), elevated Cr, CA19-9 and CEA levels were identified as independent risk factors for postoperative hyponatremia in CRC patients ($P<0.05$).

Model construction

Nomogram model: A nomogram prediction model was developed based on five indepen-

Table 1. Clinical characteristics of study population [n (%), (mean ± SD)]

Feature	Hyp group (n = 86)	NBS group (n = 194)	t/χ^2	*P*	*Shapiro-Wilk (P)*
Gender			3.222	0.073	-
Male	56 (65.12)	104 (53.61)			
Female	30 (34.88)	90 (46.39)			
Age (years)	65.74±10.86	66.82±10.09	0.784	0.434	0.216
Hypertension			2.761	0.097	-
Yes	41 (47.67)	72 (37.11)			
No	45 (54.33)	122 (62.89)			
Diabetes			3.440	0.064	-
Yes	48 (55.81)	85 (43.81)			
No	38 (44.19)	109 (56.19)			
SIADH			13.895	<0.001	-
Yes	58 (67.44)	84 (43.29)			
No	28 (32.56)	110 (56.70)			
Degree of tumor differentiation			1.910	0.167	-
Low differentiation	34 (39.53)	94 (48.45)			
Medium-high differentiation	52 (60.47)	100 (51.55)			
TNM			10.042	0.002	-
I~II	35 (40.70)	107 (55.15)			
III~IV	51 (59.30)	87 (44.85)			
Adjuvant radiotherapy/chemotherapy			3.319	0.068	-
Yes	57 (66.28)	106 (54.64)			
No	29 (33.72)	88 (45.36)			
Modus operandi			4.248	0.373	-
Dixon operation	26 (30.23)	58 (29.89)			
miles operation	23 (26.75)	54 (27.84)			
Hartmann operation	19 (22.09)	26 (13.40)			
Proctectomy	8 (9.30)	25 (12.89)			
Colectomy	10 (11.63)	31 (15.98)			
WBC (×10^9/L)	6.76±2.04	7.23±1.91	1.831	0.069	0.185
PLT (×10^9/L)	176.59±21.34	174.35±20.62	0.815	0.416	0.302
Hb (g/L)	135.82±21.27	136.41±23.59	0.203	0.839	0.257
Fib (g/L)	3.47±0.69	3.52±0.64	0.455	0.650	0.338
TBIL (μmol/L)	9.44±1.56	9.29±2.14	0.660	0.510	0.291
AST (IU/L)	25.97±4.69	25.37±4.60	0.981	0.328	0.224
ALT (IU/L)	27.33±5.76	27.56±4.68	0.331	0.741	0.275
Cystatin C (mg/L)	1.19±0.36	1.21±0.37	0.587	0.558	0.316
Cr (μmol/L)	85.57±12.11	77.14±10.92	5.535	<0.001	0.193
Urea nitrogen (mmol/L)	5.93±1.24	6.01±1.19	0.502	0.617	0.248
HDL-C (mmol/L)	1.83±0.56	1.92±0.63	1.198	0.232	0.325
LDL-C (mmol/L)	3.57±0.92	3.41±0.89	1.265	0.208	0.269
CA19-9 (U/ml)	30.36±6.27	28.45±3.65	2.634	0.010	0.178
CEA (ng/ml)	8.90±2.33	7.82±1.83	3.821	<0.001	0.209
Serum potassium (mmol/L)	3.94±0.41	3.82±0.56	1.861	0.064	0.283
Serum calcium (mmol/L)	2.16±0.34	2.24±0.29	1.684	0.094	0.307

Note: SIADH, syndrome of inappropriate antidiuretic hormone secretion; WBC, white blood cell count; PLT, platelet count; Hb, hemoglobin; Fib, fibrinogen; TBIL, total bilirubin; Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

Table 2. Multivariate logistic regression analysis of risk factors for postoperative hyponatremia

	β	S.E.	Wald	P	OR	95% CI (lower)	95% CI (upper)
SIADH	0.920	0.306	9.071	0.003	2.510	1.379	4.568
TNM	0.932	0.304	9.387	0.002	2.539	1.399	4.609
Cr	0.055	0.013	16.599	<0.001	1.056	1.029	1.085
CA19-9	0.090	0.032	7.818	0.005	1.094	1.027	1.165
CEA	0.259	0.074	12.357	<0.001	1.296	1.122	1.498
constant	-11.033	1.670	43.641	<0.001	<0.001		

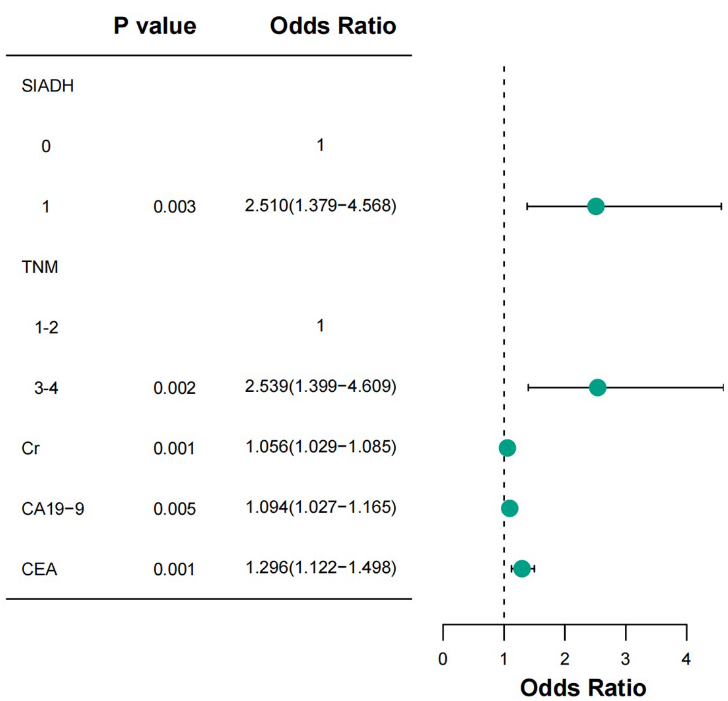

Figure 1. Forest plot of multi-factor analysis results.

dent risk factors: SIADH, TNM, Cr, CA19-9, and CEA, as shown in **Figure 2A**. The prediction formula of the model was: Y = -11.033+ 0.920*SIADH+0.932*TNM+0.055*Cr+0.090* CA19-9+0.259*CEA. In the training set, the nomogram achieved an AUC of 0.819 (95% CI: 0.756-0.882), with a sensitivity of 81.0% and a specificity of 70.3% (**Figure 2B**); in the internal validation cohort, the AUC was 0.680 (95% CI: 0.550-0.810), with a sensitivity of 80.4% and a specificity of 57.1% (**Figure 2C**). The calibration curves demonstrated good agreement between the predicted and observed probabilities in the training set (**Figure 2D**), while that in the validation set was relatively unsatisfactory, with a noticeable deviation between predicted and observed probabilities (**Figure 2E**).

Decision tree model: The decision tree model is shown in **Figure 3A**. In the training set, the AUC value was 0.832 (95% CI: 0.767-0.896), with a sensitivity of 74.1% and a specificity of 87.7% (**Figure 3B**); in the internal validation set, the AUC value was 0.695 (95% CI: 0.567-0.822), with a sensitivity of 57.1% and a specificity of 76.8% (**Figure 3C**). The calibration curve indicated that the predicted probability in the training set were close to the observed probabilities (**Figure 3D**), while that in the validation set was not very close to the actual value (**Figure 3E**).

Random forest model: A random forest model was developed, as shown in **Figure 4A**. The out-of-package error gradually stabilized when the number of decision trees reached 25. Therefore, the number of trees in final random forest was set to 25.

The variable importance in the random forest model was assessed using two commonly adopted indicators: mean decrease in Gini index (MDG) and mean decrease in accuracy (MDA). Specifically, MDG reflects the contribution of each variable to reducing node impurity during decision tree construction, while MDA quantifies the reduction in model prediction accuracy after random permutation of a given variable. Higher MDG or MDA value indicate greater predictive importance of the corresponding variable for postoperative hyponatremia in CRC patients. Based on these two metrics, the variable importance ranked in the following order of importance: CA19-9, CEA, SIADH, and TNM stage (**Figure 4B**).

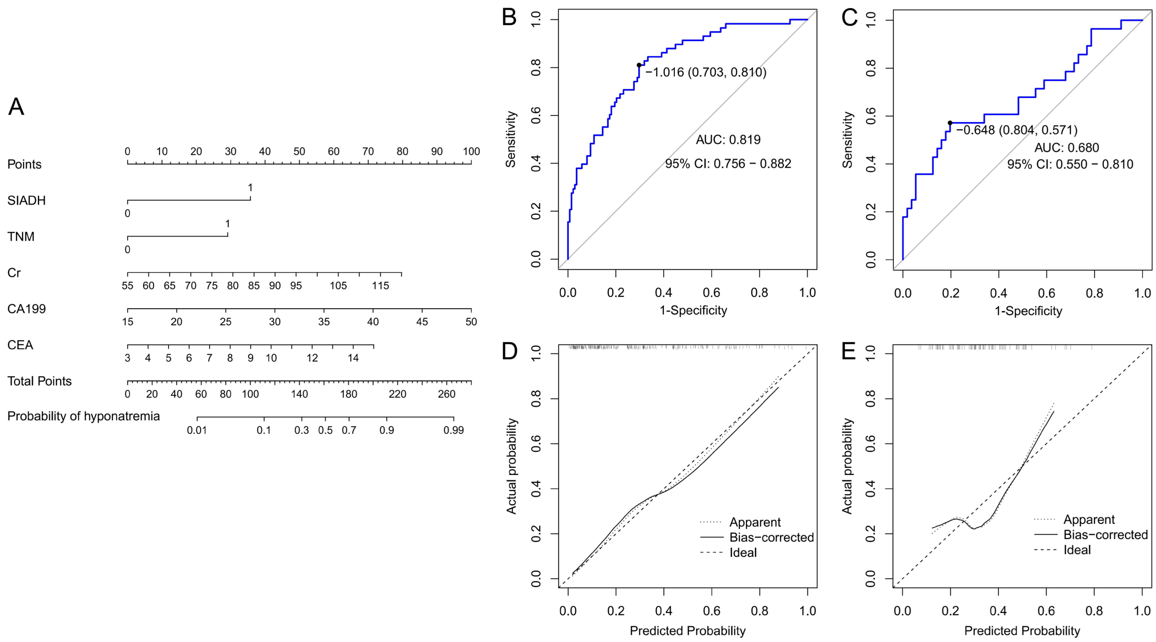

Figure 2. Nomogram model for predicting postoperative hyponatremia in CRC patients. A. Nomogram constructed based on five independent predictors. (The total score for each patient corresponds to the predicted probability of postoperative hyponatremia); B. ROC curve of the nomogram in the training set (AUC = 0.819, 95% CI: 0.756-0.882); C. ROC curve of the nomogram in the validation set (AUC = 0.680, 95% CI: 0.550-0.810); D. Calibration curve of the nomogram model in the training set; E. The calibration curve of the nomogram model in the validation set. Notes: CRC, colorectal cancer; ROC, receiver's operating characteristic; AUC, area under the ROC curve.

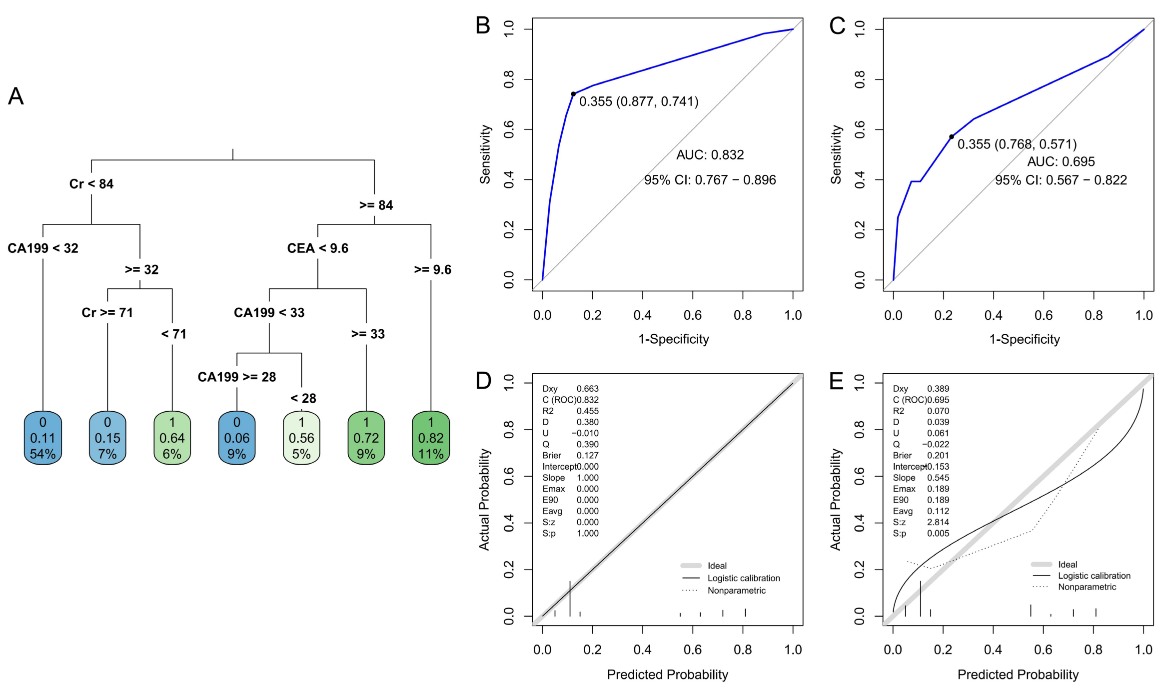

Figure 3. Decision tree model for predicting postoperative hyponatremia in CRC patients. A. Structure of the decision tree model, showing the splitting rules based on Cr, CA19-9, and CEA values; B. ROC curve of the decision tree in the training set (AUC = 0.832, 95% CI: 0.767-0.896); C. ROC curve of the decision tree in the validation set (AUC = 0.695, 95% CI: 0.567-0.822); D. Calibration curve of the decision tree the training set; E. Calibration curve of the decision tree in the validation set. Notes: CRC, colorectal cancer; ROC, receiver's operating characteristic; AUC, area under the ROC curve.

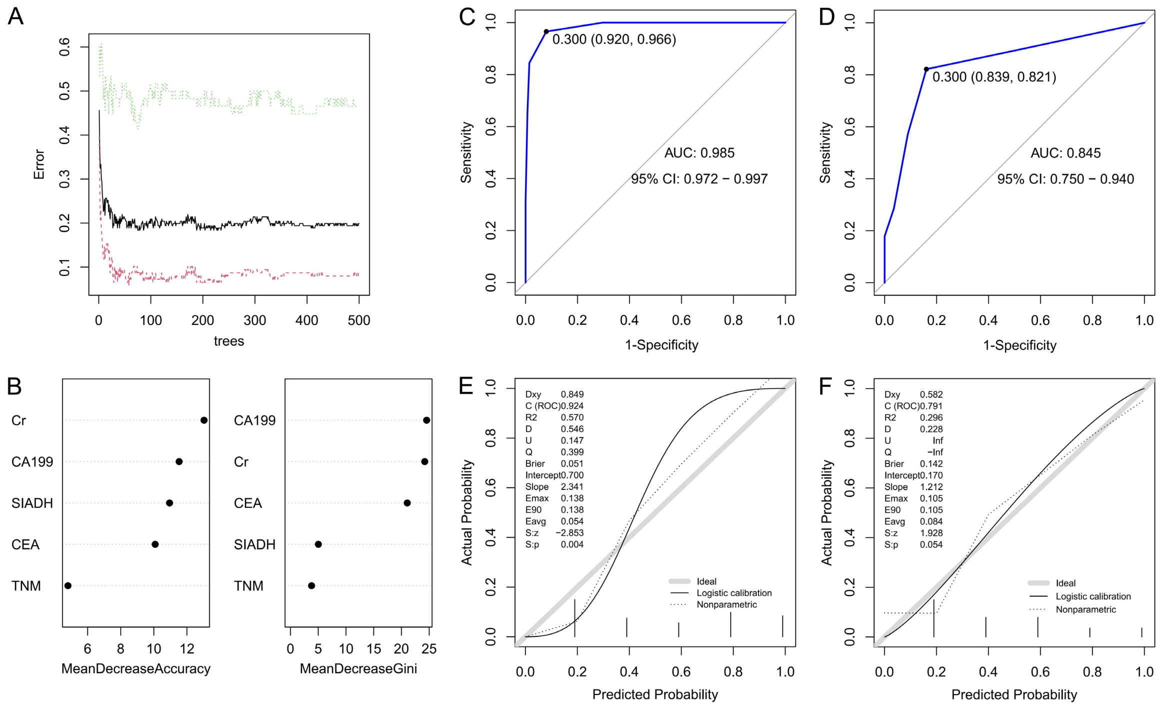

Figure 4. Random forest model for predicting postoperative hyponatremia in CRC patients. A. Relationship between the number of trees and out-of-band error in the random forest model; B. Variable importance ranking based on mean decrease in accuracy (MDA) and mean decrease in Gini index (MDG). Cr showed the highest importance, followed by CA19-9, SIADH, CEA, and TNM stage; C. ROC curve of the random forest in the training set (AUC = 0.985, 95% CI: 0.972-0.997); D. ROC curve of the random forest in the validation set (AUC = 0.845, 95% CI: 0.750-0.940); E. Calibration curve of the random forest in the training set; F. Calibration curve of the random forest in the validation set. Notes: CRC, colorectal cancer; ROC, receiver's operating characteristic; AUC, area under the ROC curve.

In the training set, the AUC value of the random forest model was 0.985 (95% CI: 0.972-0.997), with a sensitivity of 96.6% and a specificity of 92.0% (**Figure 4C**); in the internal validation set, the AUC value was 0.845 (95% CI 0.750-0.940), with a sensitivity of 82.1% and a specificity of 83.9% (**Figure 4D**). The calibration curves metrics good agreement between predicted and observed probabilities in both the training and internal validation cohort (**Figure 4E**, **4F**).

BP neural network model: A BP neural network model was developed, as shown in **Figure 5A**. The AUC value of the BP model in the training set was 0.988 (95% CI: 0.970-1.00), with a sensitivity of 96.5% and a specificity of 100% (**Figure 5B**); and in the internal validation set, the AUC was 0.559 (95% CI: 0.417-0.702), with a sensitivity of 39.3% and a specificity of 75.0% (**Figure 5C**). The calibration curve showed that good agreement between predicted and observed probabilities in the training set (**Figure 5D**), whereas that in the validation set was relatively poor, with a noticeable deviation between predicted and observed probabilities (**Figure 5E**).

Comparison of the prediction effects of the four models

The predictive performances of the four models were further compared by evaluating sensitivity, specificity, and AUC. Among the four models, the random forest model demonstrated superior sensitivity, specificity and AUC values in both the training and validation sets, as shown in **Table 3**. The results from the external validation set (**Table 4**) further confirmed the superiority of the random forest model, demonstrating a significantly higher prediction accuracy (85.11%) compared to Nomogram (65.96%), Decision tree (74.47%), and BP neural network (70.21%).

The BP neural network exhibited substantial overfitting, as evidenced by the marked discrepancy between training and validation performance. Although L2 regularization, early

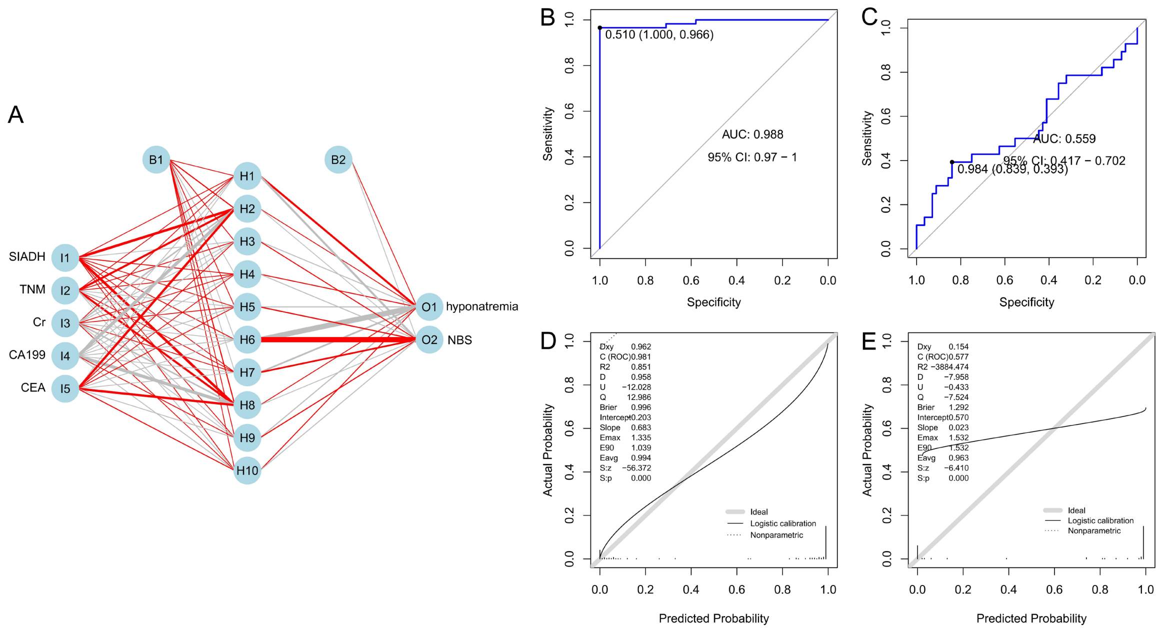

Figure 5. BP neural network prediction model for predicting postoperative hyponatremia in CRC patients. A. Structure of the BP neural network, including the input layer (5 variables), hidden layer (10 neurons), and output layer (2 nodes for hyponatremia and normal sodium); B. ROC curve of the BP neural network in the training set (AUC = 0.988, 95% CI: 0.970-1.00); C. ROC curve of the BP neural network in the validation set (AUC = 0.559, 95% CI: 0.417-0.702); D. Calibration curve of the BP neural network in training set; E. Calibration curve of the BP neural network in validation set. Notes: CRC, colorectal cancer; ROC, receiver's operating characteristic; AUC, area under the ROC curve.

Table 3. Comparison of predictive performance among the four models

Dataset	Evaluating indicator	Nomogram	Decision tree	Random forest	BP neural network
Training sets	Sensitivity (%)	81.0%	74.1%	96.6%	96.5%
	Specificity (%)	70.3%	87.7%	92.0%	100%
	AUC (95% CI)	0.819 (0.756-0.882)	0.832 (0.767-0.896)	0.985* (0.972-0.997)	0.988 (0.970-1.00)
	Youden index	0.513	0.618	0.886	0.965
	Accuracy (%)	75.65	80.90	94.30	98.25
Internal validation set	Sensitivity (%)	80.4%	57.1%	82.1%	39.3%
	Specificity (%)	57.1%	76.8%	83.9%	75.0%
	AUC (95% CI)	0.680 (0.550-0.810)	0.695 (0.567-0.822)	0.845* (0.750-0.940)	0.559 (0.417-0.702)
	Youden index	0.375	0.339	0.660	0.143
	Accuracy (%)	68.75	66.95	83.00	57.15

Note: *P<0.05, compare with the other three models.

stopping, and cross-validation were applied to improve model generalization, the validation performance remained unsatisfactory. Given the relatively small sample size, the BP model lacked sufficient robustness and stability. Therefore, the random forest model was selected as the optimal predictive model due to its consistent performance across all datasets.

To evaluate the clinical utility of random forest model, DCA was performed in both the training and validation sets. The DCA curves showed that, within a threshold probability range of approximately 0.05 to 0.85 in the training set and 0.05 to 0.75 in the validation set, the model provided greater net clinical benefit than both the "treat all" and "treat none" strategies (**Figure 6**). This finding indicates that the model has good clinical applicability for predicting postoperative hyponatremia in CRC patients and can effectively guide clinical decision-making.

Table 4. The confusion matrix of the external validation set

		Predicted Value							
		Nomogram		Decision tree		Random forest		BP	
		Hyp	NBS	Hyp	NBS	Hyp	NBS	Hyp	NBS
Actual Value	Hyp (n = 16)	11	5	10	6	13	2	8	8
	NBS (n = 31)	11	20	6	25	4	27	6	25

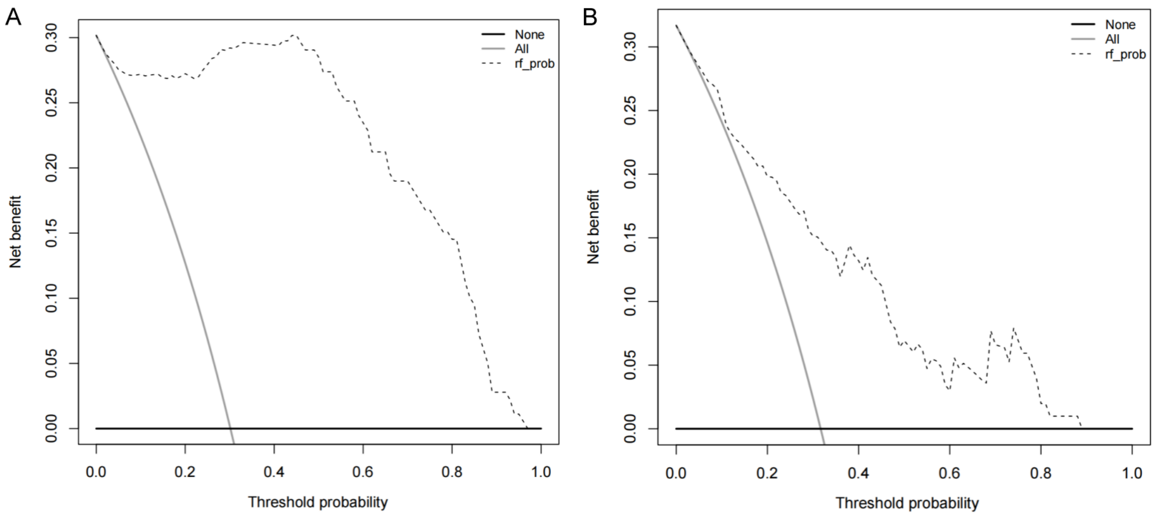

Figure 6. DCA of the random forest model for predicting postoperative hyponatremia in CRC patients. A. DCA curve of the random forest model in training set; B. DCA curve of the random forest model in validation set. The black line represents the "treat none" strategy, the gray line represents the "treat all" strategy, and the dashed line represents the random forest prediction model. Within a reasonable range of threshold probabilities, the random forest model achieved a higher net clinical benefit than either of the two extreme strategies. Notes: CRC, colorectal cancer; DCA, decision curve analysis.

Discussion

Hyponatremia is a common complication in CRC patients, with an incidence of 27.6% [17, 18]. The severity of hyponatremia is closely associated with mortality risk, and even mild hyponatremia is linked to increased long-term mortality. Selmer C et al. reported that the risk of death in patients with hyponatremia increased progressively with the decrease of serum sodium level. Compared with individuals with normal serum sodium levels, mild, moderate, and severe hyponatremia were associated with 81%, 111%, and 152% increases in all-cause mortality, respectively [19]. In addition, hyponatremia has been shown to be significantly associated with long-term mortality in patients with acute coronary syndrome. A meta-analysis showed that the risk of long-term mortality in patients with hyponatremia was 74% higher than that in patients with normal serum sodium [20]. Postoperative hyponatremia in patients with CRC may substantially compromise patient prognosis and postoperative recovery [21]. It is of great significance to identify risk factors associated with postoperative hyponatremia and establish an effective predictive model for early intervention and individualized preoperative management.

Hyponatremia in cancer patients is associated with advanced age, multiple comorbidities, advanced TNM stage, SIADH during chemotherapy or radiotherapy, and deterioration of biochemical parameters [22, 23]. In this study, SIADH was identified as an independent risk factor for postoperative hyponatremia in CRC patients. The incidence of SIADH in these patients may be related to surgical stress response, postoperative fluid management, drug use, tumor-related factors, and endocrine dysfunction. Abnormal elevation of antidiuretic hormone (ADH) can impair renal water and sodium regulation [24]. Advanced TNM stage

(III~IV) was also identified as a risk factor for hyponatremia in CRC patients. Previous studies have confirmed that TNM stage is closely associated with survival and prognosis in patients with CRC [25]. Patients with TNM stage III~IV disease are more likely to develop postoperative hyponatremia [26]. Patients with advanced-stage cancer often experience cachexia, loss of appetite, nausea, and vomiting, which may lead to inadequate sodium intake and increased gastrointestinal loss. Furthermore, fluid depletion can stimulate non-osmotic ADH secretion, resulting in excessive water reabsorption by the kidneys and subsequent dilutional hyponatremia. With increasing TNM stage, the survival rate of CRC patients gradually decreases and prognosis worsens, further supporting the predictive value of TNM staging [27, 28].

In addition, this study also found that elevated Cr was an independent risk factor for postoperative hyponatremia in CRC patients. Clinical monitoring of serum Cr is beneficial for early identification of postoperative complications, including hyponatremia, in patients with CRC. Previous studies have shown that impaired renal function may disrupt water and electrolyte homeostasis, thereby increasing the risk of hyponatremia [29, 30].

CA19-9 and CEA are tumor markers widely used for the diagnosis and survival analysis in CRC patients. Both CA19-9 and CEA have been identified as independent risk factors for colorectal prognosis [31, 32]. CA19-9 is a carbohydrate-associated tumor marker commonly used as an auxiliary diagnostic indicator for digestive tract tumors. CEA is an acidic glycoprotein broadly used for auxiliary diagnosis, efficacy monitoring, and recurrence surveillance. Elevated CEA levels have been reported in a variety of malignancies, including CRC, gastric cancer, pancreatic cancer [33]. In this study, serum levels of CA19-9 and CEA were significantly higher in the hyponatremia group and were identified as independent risk factors for postoperative hyponatremia in CRC patients. Elevated CA19-9 and CEA levels typically indicate a higher tumor burden, which could indirectly contribute to postoperative electrolyte imbalance and poor nutritional status. Therefore, in clinical practice, these indicators and other clinical information should be comprehensively evaluated to facilitate individualized perioperative management and monitoring plans.

Machine learning techniques have shown great potential in disease prediction and clinical decision support. In a study investigating machine learning methods for predicting CRC prognosis [34], random forest model outperformed generalized linear models and the neural networks in predicting the binary outcomes of disease recurrence and treatment response, with accuracy rates of 0.71 and 0.70 respectively; furthermore, this model achieved favorable C-index values (0.86 and 0.76) for predicting overall survival and disease-free survival, indicating its high discriminatory ability in predicting CRC prognosis.

In this study, five significant variables (SIADH, TNM, Cr, CA19-9 and CEA) were included in the four predictive algorithms, namely the nomogram, random forest, decision tree, and BP neural network models, to develop predictive models for postoperative hyponatremia in CRC patients. The results showed that the random forest model showed the best overall performance among the four models in both the training and external validation sets. These findings indicate that the random forest model possesses excellent predictive capability and generalizability for identifying CRC patients at high risk of postoperative hyponatremia. It is noteworthy that conventional statistical analysis methods may have limited capability in handling large-scale and complex medical datasets, while machine learning algorithms exhibit advantages in processing multidimensional and nonlinear data structures. The random forest algorithm can automatically evaluate variable importance, is not restricted by strict assumptions regarding predictor distributions, and is capable of simultaneously processing both continuous and categorical variables.

Several limitations of this study should be acknowledged. First, this was a single-center retrospective study with a relatively limited sample size, which may have introduced selection bias and restricted the generalizability of the findings. Although an external testing cohort was included, the sample size of the external validation cohort remained relatively small. Future multi-center studies with larger sample sizes are warranted to further validate and optimize the predictive models constructed in this study.

Second, the BP neural network model constructed in this study exhibited a substantial overfitting. Specifically, the AUC of the training set reached 0.988, while that of the validation set was only 0.559, indicating poor generalizability. This phenomenon is quite common in neural network modeling, especially when the sample size is limited and the model complexity exceeds the information capacity of the dataset. To address this issue, grid search combined with 5-fold cross-validation was performed, and hidden-layer structures containing 1-15 neurons were evaluated. Finally, a simplified single hidden-layer structure with 10 neurons was selected instead of the initial 15-neuron configuration. Although the overfitting degree was alleviated after simplification, the validation performance remained unsatisfactory.

Conclusion

The random forest-based predictive model developed in this study showed favorable predictive performance for identifying the risk of hyponatremia in CRC patients. By integrating key risk factors, the model may provide important decision support for clinicians, including preoperative risk assessment, personalized treatment plan, multidisciplinary collaboration. The model may facilitate the early identification of high-risk patients and assist in the implementation of preventive measures, thereby potentially improving postoperative management and patient outcomes.

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Disclosure of conflict of interest

None.

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