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Development of a nomogram for predicting the outcome in patients with prolonged disorders of consciousness based on the multimodal evaluative information

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Abstract

Objective To establish a nomogram prediction model for the patients with prolonged disorders of consciousness (PDOC) caused by brain injury at six months based on behavioral scale scores, neuroelectro-physiological techniques and hypothalamic-pituitary hormone levels.

Methods The clinical data of patients with PDOC who were first diagnosed and hospitalized in the Department of Rehabilitation Medicine of The Affiliated Jiangning Hospital of Nanjing Medical University from March 2023 to July 2024 were collected retrospectively. We performed stratified sampling based on etiology and divided into a training set (121 cases) and a validation set (49 cases) in a ratio of 7:3. After a 6-month follow-up, patients were divided into groups with improved consciousness and those without improved consciousness based on changes in CRS-R scores.Clinical behavioral scores, somatosensory evoked potentials, brainstem auditory evoked potentials, and levels of hypothalamic-pituitary hormones were utilized to identify prognostic factors for prolonged disorders of consciousness. Concurrently, a nomogram prediction model was crafted and validated to forecast the prognosis of patients with prolonged disorders of consciousness. Decision curve analysis (DCA) was subsequently employed to appraise the clinical applicability of this predictive model.

Results The comparison of clinical data between the training and validation cohorts revealed no significant statistical disparities ($P > 0.05$). Within the training cohort of 121 PDOC patients, 63 (52.1%)PDOC patients exhibited enhanced consciousness levels. Similarly, in the validation cohort of 49 PDOC patients, 25 (51%) PDOC patients showed improvements in consciousness. Utilizing a combination of random forest analysis, LASSO regression, and multivariate Logistic regression, we identified four key predictive variables: CRS-R score (OR = 1.05, 95%CI 1.02–1.08, $P = 0.002$), BAEP grading(OR = 0.88, 95%CI 0.79–0.98, $P = 0.02$), N60 classification (OR = 1.22, 95%CI 1.01–1.48, $P = 0.02$), and Estradiol (OR = 1.01, 95%CI 1.00–1.02, $P = 0.01$). The area under the curve (AUC) for the predictive model in the training set was 0.919(95%CI 0.87–0.968),while in the validation set, it was 0.888(95%CI 0.796–0.98). The calibration curves demonstrated a high degree of concordance between predicted probabilities and actual results, suggesting

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that the model possesses strong discriminative power and calibration accuracy. Furthermore, in the context of clinical decision-making, Decision Curve Analysis indicated a superior net benefit for our predictive model.

Conclusion The nomogram model, which integrates CRS-R score, BAEP grading, N60 classification and Estradiol, provides a comprehensive assessment of short-term prognosis in patients with prolonged disorders of consciousness, demonstrating high accuracy.

Keywords Disorder of consciousness, Brain injury, Minimally conscious state, Vegetative state, Cohort

Introduction

As emergency and critical care medicine has made rapid strides, the survival rate of patients with brain injuries has markedly improved, resulting in a significant rise in the prevalence of disorders of consciousness (DOC). In China, it is estimated that there are between 300,000 and 500,000 individuals with DOC, with over 70,000 new cases reported annually. This translates to an annual medical expenditure of 30 to 50 billion yuan [1], imposing a considerable burden on both the caregivers and families of DOC patients, and sparking numerous ethical and legal concerns [2]. Within the first year following the emergence of consciousness disorders, the mortality rate stands at a staggering 35%, with only 40% of patients experiencing any improvement in their level of consciousness [3]. There is an urgent need for early, objective, and precise prognostic assessments, as these will significantly impact future medical decisions.

The Coma Recovery Scale-Revised (CRS-R) is recognized as the preeminent clinical tool for the structured assessment of patients with disorders of consciousness, showcasing robust reliability and validity. Nonetheless, complications such as severe movement disorders, aphasia, endotracheal intubation, and fluctuations in arousal levels can impede behavioral evaluations, resulting in a misdiagnosis rate that reaches up to 43% [4]. Neuroelectrophysiological assessments are straightforward to conduct and enable continuous, real-time monitoring at the bedside. They offer critical insights into the extent and severity of brain damage, potentially aiding in the prognostic determination for individuals with disorders of consciousness.

The bilateral absence of N20 waves in Somatosensory Evoked Potentials (SEPs) post-median nerve stimulation serves as an early marker for poor prognosis in patients with anoxic coma, albeit with limited sensitivity [5, 6]. The short-latency SEP are primarily concerned with evaluating the integrity of sensory pathways and their corresponding cortical regions, excluding the secondary processing within higher-order cortical networks, which renders their prognostic significance a matter of debate [7–10]. Middle-Latency Somatosensory Evoked Potentials (MLSEP), such as N35, N60, and N70, are capable of reflecting the integrity of secondary cortical networks and could be potential indicators of consciousness recovery in patients with disorders of consciousness [11, 12]. Nevertheless, the sensitivity and specificity of MLSEP in prognostic assessment are less than ideal, potentially attributable to variations in sample size and timing of prediction [11, 13–16]. Furthermore, research on the prognostic implications of evoked potentials in PDOC patients is scarce, leaving the clarity of their prognostic value undetermined.

Furthermore, neuroendocrine disorders are commonly observed in patients with brain injuries [16–21]. A study found that neuroendocrine disorders affect cognitive functions such as attention, memory, and executive ability in post-brain injury patients [22]. Additionally, a study has demonstrated substantial correlations between sex hormone levels and the Glasgow Outcome Scale extended (GOSE), with sex hormones showing a positive correlation and IGF-1 a negative correlation with GOSE scores [23]. These findings highlight the potential influence of neuroendocrine functions on the prognosis of patients with prolonged disorders of consciousness.

Consequently, this study endeavors to uncover prognostic factors associated with prolonged disorders of consciousness by leveraging clinical baseline information, behavioral evaluations, neuroelectrophysiological assessments, and hypothalamic-pituitary hormonal levels. Furthermore, it seeks to develop a predictive model that facilitates a visual and probabilistic prognosis assessment for patients grappling with prolonged disorders of consciousness.

Materials and methods

Patients

We conducted a retrospective analysis of 170 patients with prolonged disorders of consciousness treated in the Department of Rehabilitation Medicine of The Affiliated Jiangning Hospital of Nanjing Medical University from March 2023 to July 2024. The inclusion criteria were as follows: (i) aged 18–75 years; (ii) severe trauma, hypoxia, or vascular brain injury; (iii) a clinical diagnosis of VS (Vegetative State) or MCS (Minimally Conscious State) made by the Chinese version of the Coma Recovery Scale-Revised (CRS-R) [24, 25]; (IV) 1–3 months post-injury; and (V) stabilized medical clinical conditions. Patients with mixed etiology (e.g., traumatic and anoxic brain injury) or a premorbid history of psychiatric

or neurodegenerative diseases were excluded. Exclusion criteria included: (I) Unstable vital signs such as severe heart failure or respiratory failure; (II) previous history of brain injury or neurodegenerative disease; (III) use of sedatives drugs, antiepileptic drugs, and nerve excitation drugs; (IV) known hearing impairment; and (V) incomplete clinical data.

Note Clinical evaluations were performed bedside, facilitated by caregivers who provide significant stimulation to the patients. The registration of information was the responsibility of three physicians participating in the study, who also managed the clinical care of the patients.

Sample size Estimation

We relied on the Events Per Variable criterion (EPV), particularly EPV ≥ 10, to determine the minimum sample size required [26]. With four independent variables selected and 40% of patients showing clinical improvement [3], the minimum sample size calculated was 100. Considering a dropout rate of 20% during the study period, a minimum of 120 participants were required.

Clinical evaluation

We collected clinical data on the age, gender, etiology, duration of ICU stay, decompressive craniectomy status, history of hypertension, history of diabetes, history of coronary heart disease, and CRS-R scores of patients with prolonged disorders of consciousness.

Brainstem Auditory Evoked Potentials (BAEP) and upper limb somatosensory evoked potentials were recorded following standard laboratory protocols [27, 28], utilizing the Neuron-Spectrum-4 electromyography and evoked potential instrument manufactured by the Russian neurosoft company. Cortical SEPs were deemed present if they were observed either bilaterally or unilaterally. Conversely, SEPs were classified as absent in cases where no bilateral SEPs were detected. BAEP grading followed the Hall classification [29]: Grade 1, normal; Grade 2, slightly abnormal, exhibiting moderate waveform differentiation, with possible issues such as prolonged peak latency of the I, III, or (and) V waves, prolonged interpeak latency of the I–III, III–V, or (and) I–V waves, peak-to-peak latency ratio of III–V/I–III > 1, and amplitude ratio of V/I < 0.15; Grade 3, moderate abnormality, featuring poor waveform differentiation and repeatability, with possible issues such as prolonged peak latency of the III or V waves, or disappearance of the V wave; and Grade 4, severe abnormality, characterized by only the I wave's presence or the disappearance of all waveforms.

We collected the following hormone levels from patients with prolonged disorders of consciousness (PDOC)within 48 h of admission: cortisol, adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and estradiol (E2).

Outcome definition

All PDOC patients were categorized into Vegetative State (VS)/Unresponsive Wakefulness Syndrome (UWS), Minimally Conscious State (MCS) based on repeated CRS-R scores. Clinical diagnosis of UWS/VS was assigned when patients exhibited a sleep-wake cycle, autonomic nerve and motor reflexes, but lacked self or environmental signs of conscious behavior [30]. Patients may transition to MCS [31], characterized by clear signs of consciousness and behavior, such as following simple commands and responding to harmful stimuli. Consideration for emergence from MCS was given if patients could functionally communicate or use objects. After a 6-month follow-up, patients were classified as "improved" if they transitioned from MCS to eMCS, or from VS/UWS to MCS, or if they ultimately regained consciousness. Patients were classified as "NO improved" if MCS patients at baseline regressed to VS/UWS, showed no improvement, or died [32].

Statistical analysis

The data were analyzed and processed using R software(version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria); The specific R packages "caret", "rfPermute", "glmnet", "rms", "pROC"and "rmda" were used for model construction and validation.Normally distributed continuous variables were presented as mean ± standard deviation and compared using independent sample t-tests. Non-normally distributed data were presented as median (interquartile range) and analyzed using the Kruskal-Wallis rank-sum test. Categorical variables were expressed as frequency (percentage) and compared using the chi-square test or Fisher's exact probability.

This study retrospectively analyzed clinical data from 170 patients with PDOC. Collected parameters included 17 electrophysiological and biochemical measures. The raw data underwent dual-independent verification before being entered into an Excel database. Data cleaning was performed using R software, with exclusion of variables showing > 10% missing values. Through the "caret "package (v6.0-94), stratified sampling was implemented with stratification by etiology, dividing the cohort into training ($n = 121$) and validation ($n = 49$) sets at a 7:3 ratio.The training set was utilized for feature selection and model construction, while the validation set was employed to evaluate the model's effectiveness. Inter-group comparability was confirmed by chi-square tests ($p > 0.05$).

Random forest for Variable Selection: Importance assessment was performed using the "rfPermute"package

(v2.5.1) to construct a permutation-based random forest model. The number of decision trees (number of trees[ntree] = 134) was determined by monitoring the stability of the Out-of-Bag (OOB) error. When the number of trees exceeded 100, the fluctuation range of the OOB error remained below 0.5%, indicating model convergence. Parallel computing was implemented with num. cores = 3 to accelerate the analysis.

Permutation tests were employed to generate p-values by simulating a random distribution, with the precision of these estimates directly dependent on the number of permutations (nrep = 134). Variable importance was assessed based on the mean decrease in accuracy (Mean Decrease Accuracy), and statistical significance was defined as $p < 0.05$.After correcting for multiple testing bias using permutation-derived p-values, nine candidate variables were selected for subsequent analysis based on their ranked importance.

Lasso Regression for variable selection was performed using L1-regularized regression (alpha = 1) implemented in the"glmnet"package (v4.1-7). The optimal penalty parameter (λ) was determined via 10-fold stratified cross-validation, with λ.min selected to minimize the cross-validated deviance, ensuring an optimal trade-off between model fit and overfitting risk. Following variable compression, four core predictors were retained based on non-zero coefficients: CRS-R score, BAEP grading, Estradiol, N60 classification.The variable selection process was visualized using elastic net coefficient paths, and multicollinearity was assessed via variance inflation factors (VIFs), all of which were < 5, confirming the absence of significant collinearity among selected predictors.A forced-entry multivariable logistic regression model was built using the selected predictors. odds ratios (ORs) and 95% confidence intervals (95%CI)were computed via the"rms"package(v6.7-0), with results visualized in a nomogram. Akaike Information Criterion (AIC) for the optimally parsimonious model (AIC = 82.3) was presented as a clinically interpretable nomogram for individualized outcome prediction.

We conducted comprehensive validation of model performance across three key domains - discrimination, calibration, and clinical utility - through both training set and independent validation set validation approaches. ROC curve analysis was performed using the "pROC" package (v1.18.2). We calculated: Area under the curve (AUC) with 95% CI(DeLong's method), Optimal cutoff determined by Youden's index (sensitivity + specificity-1);Internal validation: AUC computation on training set($n = 119$) with 10-fold cross-validation; External validation: Independent testing on validation cohort ($n = 51$) without model refitting.Calibration curves were assessed via 1,000 bootstrap resamples, with LOESS smoothing to evaluate agreement between predicted and observed probabilities.Overall prediction accuracy was quantified using the Brier score (range: 0–1).Internal validation: Calibration curves were plotted for the training set.External validation: Curves were generated for the validation set to test calibration on new data. Decision Curve Analysis(DCA) was performed using the "rmda"package(v1.6), calculating net benefit across threshold probabilities (5-95%);The clinically actionable range was highlighted via shaded regions. Internal validation: Initial net benefit estimation; External validation: Confirmation of clinical applicability.Finally, We developed an interactive interface for the final model was established based on the validation set to facilitate clinical evaluation applications.

Results

Baseline data

A total of 170 patients with PDOC were included in the final analysis (Fig. 1). The demographic and clinical characteristics of the training and validation sets are summarized in Table 1. After a 6-month follow-up, 88 patients (51.8%) showed an improvement in their level of consciousness; in the raining set, there were 121 patients with an average age of 60.11 ± 12.01 years and a CRS-R score of 10.17 ± 4.14 points; 63 patients (52.1%) showed an improvement in their level of consciousness. In the validation set, there were 49 patients with an average age of 57.61 ± 11.78 years and a CRS-R score of 9.41 ± 3.85 points; among them, 25 patients (51%) showed an improvement in their level of consciousness.

Identify predictors

Using the random forest method, 27 independent variables were screened, and ultimately 9 variables were identified as statistically significant (**$P < 0.01$, *$P < 0.05$). After testing and adjustment, when ntree = 134, nreo = 134, and num.cores = 3, the top most important feature variables were determined to be CRS-R score, Diagnosis, BAEP grading, Estradiol, Etiology, N60 classification, Cortisol, TSH, and N20 classification(Fig. 2).

Using the Lasso regression model, 9 characteristics were tested for their ability to predict the clinical outcomes and to avoid overfitting. The Lasso coefficient profiles of features and the optimal penalization coefficient lambda + 1se are shown in Fig. 3. The feature selection results revealed that nine variables, including CRS-R score, Diagnosis, BAEP grading, Estradiol, Etiology, N60 classification, Cortisol and N20 classification, could be used to predict clinical prognosis for PDOC patients.

Finally, the findings from the random forest analysis and lasso regression analysis were synergistically combined to identify the six most influential predictors of recovery in consciousness levels: CRS-R score, Diagnosis, BAEP grading, Estradiol, N60 classification and TSH.

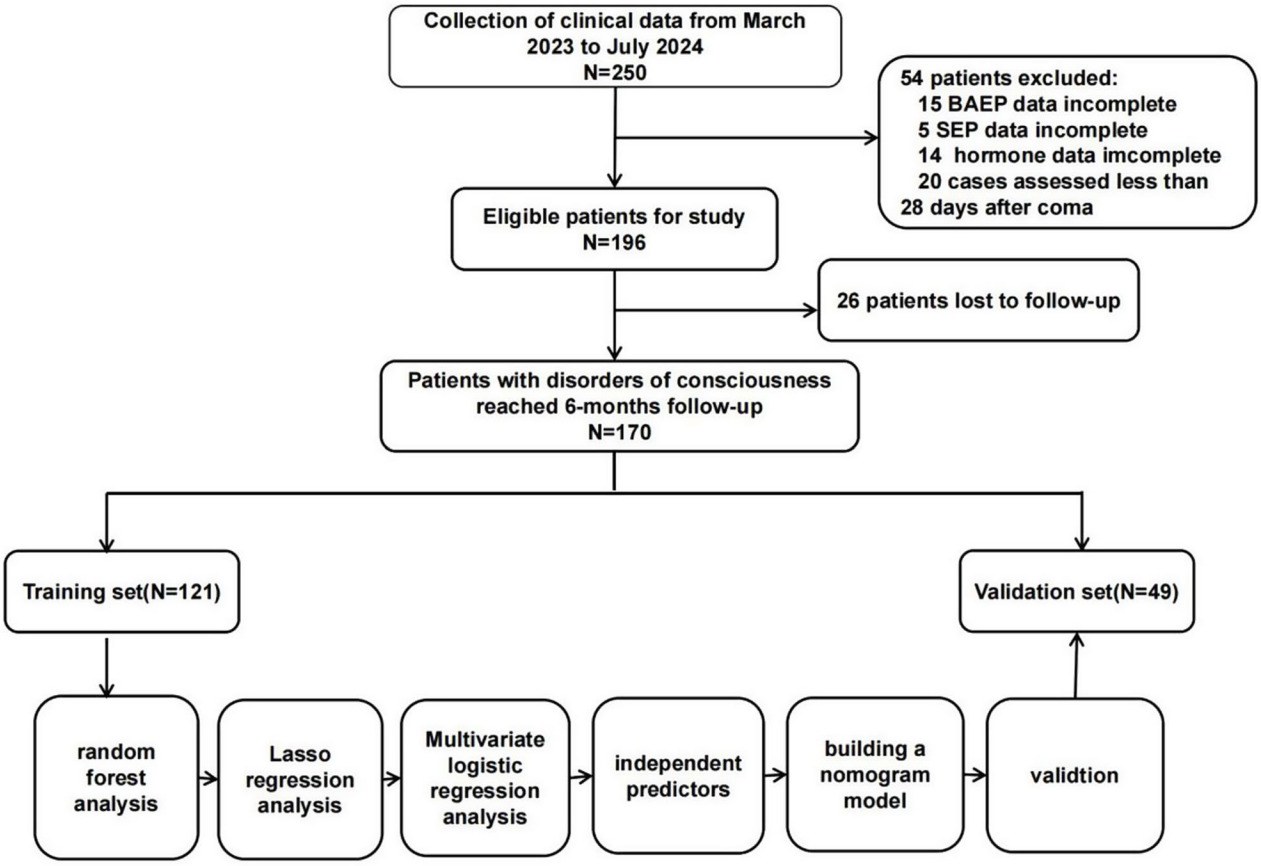

Fig. 1 Flow chart of patient enrollment

These predictors were further examined through multivariate logistic regression in Table 2.

Construction of clinical prediction model

Based on the results of multivariate logistic regression analysis, a nomogram model was constructed for predicting the 6-month prognosis of patients with PDOC using CRS-R score, BAEP grading, N60 classification and estradiol (Fig. 4). The nomogram consists of variable names and tick marks. Points in the first row can calculate the single score of each prognostic factor. Lines 2–5 represent the specific classification of each prognostic factor, with scores calculated separately according to the first row. The total points in the sixth row represent the sum of scores from all prognostic factors. The individual prognostic score of each factor for a patient is determined by adding up the total score. Line 7 indicates the clinical prognosis prediction of DOC patients. To obtain the corresponding clinical improvement probability of the patient, a vertical line is drawn based on the total score of the patient (Fig. 4).

The independent risk factors included in the nomogram were validated using the R packages (caret, rfPermute, rms, glmnet, pROC, rmda) to draw the receiver operating characteristic curve. The AUC values of the training set and the validation set were 0.919(95%CI 0.87–0.968) and 0.888(95%CI 0.796–0.98), respectively(Fig. 5A and B).Thus, the nomogram achieved a C-index of 0.888 in the validation set.

Nomogram model calibration and decision curve

In order to assess the consistency between the actual risk and predicted risk of the model, calibration curves were plotted, demonstrating a high degree of consistency between the observed and predicted probabilities of consciousness recovery in PDOC patients(Fig. 6A and B).

The blue calibration curve represents the predicted proportion of the clinical outcome to the probability of the actual outcome. The dashed black line indicates that the actual risk is equal to the predicted risk.

As shown in Fig. 7 (A and B), the DCA plots showed that the logistic model was clinically useful and had good predictive ability in the training set. Additionally, the fluctuation observed at the end of the prediction model curve may be attributed to the relatively small sample size.

We have successfully developed a user-friendly clinical interactive interface designed for the short-term

Table 1 Demographic and clinical characteristics of the patients in two group

Factors	Classify	Training set(121)	Validation set(49)	*P*
Age(years)		60.11 ± 12.01	57.61 ± 11.78	0.22
Sex	Female	41(33.9%)	*18(36.7%)*	0.73
	Male	80(66.1%)	31(63.3%)	
Smoke history	NO	61(51.4%)	*22(44.9%)*	0.32
	YES	60(49.6%)	*27(55.1%)*	
Drink history	NO	64(52.9%)	*24(49.0%)*	0.39
	YES	57(47.1%)	*25(51.0%)*	
Hypertension history	NO	26(21.5%)	*7(14.3%)*	0.19
	YES	95(78.5%)	*42(85.7%)*	
Diabetes history	NO	98(81.0%)	*42(85.7%)*	0.31
	YES	23(19.0%)	*7(14.3%)*	
Coronary heart disease	NO	106(87.6%)	*43(87.8%)*	0.60
	YES	15(12.4%)	*6(12.2%)*	
Decompressive Craniotomy	NO	54(44.6%)	*22(44.9%)*	0.47
	YES	67(55.4%)	*27(55.1%)*	
Etiology				
Trauma		31(25.6%)	*12(24.5%)*	0.99
Stroke		76(62.8%)	32(65.3%)	
Anoxia		14(11.6%)	5(10.2%)	
Diagnosis				
Vegetative State		80(66.1%)	26(53.1%)	0.08
Minimally Conscious State		41(33.9%)	23(46.9%)	
Improved outcome	NO	58(47.9%)	24(49.0%)	0.52
	YES	63(52.1%)	25(51.0%)	
N20 classification	NO	31(25.6%)	13(26.5%)	0.52
	YES	90(74.4%)	36(73.5%)	
	YES	87(73.1%)	34(66.7%)	
N60 classification	NO	47(38.8%)	19(38.8%)	0.59
	YES	74(61.2%)	30(61.2%)	
Brainstem Auditory Evoked Potentials grading				
Level 1		17(14.0%)	5(10.2%)	0.62
Level 2		57(47.1%)	29(59.2%)	
Level 3		42(34.7%)	13(26.5%)	
Level 4		5(4.1%)	2(4.1%)	
The duration of ICU(days)		24.67 ± 14.24	25.31 ± 10.57	0.78
Course (days)		91.55 ± 46.64	96.86 ± 42.39	0.49
CRS-R score		10.17 ± 4.14	9.41 ± 3.85	0.27
Progesterone(ng/mL)		0.72 ± 0.28	0.67 ± 0.33	0.33
Testosterone(nmol/L)		6.51 ± 5.69	6.69 ± 6.19	0.85
Prolactin(ng/mL)		25.39 ± 14.79	23.88 ± 13.99	0.54
Estradiol (pg/mL)		26.98 ± 12.17	28.01 ± 11.79	0.62
Luteotropichormone(IU/ L)		10.26 ± 8.52	12.01 ± 10.78	0.26
Follicle-stimulating hormone(IU/L)		18.78 ± 17.21	19.21 ± 18.44	0.89
Cortisol (nmol/L)		467.94 ± 141.66	434.22 ± 135.34	0.16
Adreno-cortico-tropic-hormone(pg/mL)		49.16 ± 26.09	44.47 ± 21.61	0.27
Free triiodothyronine (pmol/L)		3.56 ± 0.88	3.42 ± 0.75	0.34
Free teraiodothyronine (pmol/L)		16.79 ± 3.37	15.97 ± 3.08	0.14
Thyroid-stimulating hormone (mIU /L)		3.18 ± 2.03	4.09 ± 3.65	0.11

Data are expressed as n (%), mean ± SD, median (IQR), as appropriate

prognosis prediction of patients with prolonged disorders of consciousness. This tool enables medical professionals to conveniently determine the 6-month prognosis for PDOC patients with ease and efficiency; We also provide a website for the convenience of clinical doctors to use, and the interface is shown in Fig. 8.

Discussion

In this study, we developed a nomogram using CRS-R score, BAEP grading, N60 classification and estradiol in Fig. 4, which achieved a C-index of 0.888 in the validation set, indicating a good fit and suitability for clinical outcomes of patients with Prolonged Disorders of Consciousness after a 6-month follow-up. The ROC curves for this nomogram's prognosis prediction are presented in Fig. 5.Calibration and decision curve analysis demonstrated that clinicians can benefit from the decision-making supported by this model.

The main etiologies of PDOC include traumatic brain injury, ischemic stroke, hemorrhagic stroke, or hypoxic-ischemic disease. The recovery of consciousness in DOC patients varies according to the etiology [33]. Compared with patients with non-traumatic injuries, patients with traumatic injuries are more likely to recover consciousness [34, 35]. Our analysis revealed that etiology was not an independent predictor in this study, potentially reflecting the uneven distribution of etiologies within our patient cohort. Specifically, stroke cases were disproportionately represented compared to traumatic brain injuries, which may have influenced the statistical significance of etiology as a standalone predictor.Additionally, age, course of disease, and ICU stay were not significantly correlated with prognosis. This may be due to selection bias and limited sample size, and further studies with larger sample sizes are needed to verify these findings. After taking into account the etiology, age, course of disease and Coma Recovery Scale-Revised (CRS-R) scores remain significant prognostic factors for DOC patients [36–38]. Our study also supports that higher CRS-R scores are associated with better clinical outcomes, which aligns with findings from previous research [39, 40].

Damage to the brainstem ascending reticular activating system is one cause of disorders of consciousness. The severity of brainstem injury is closely correlated with the level of consciousness. Brainstem auditory evoked

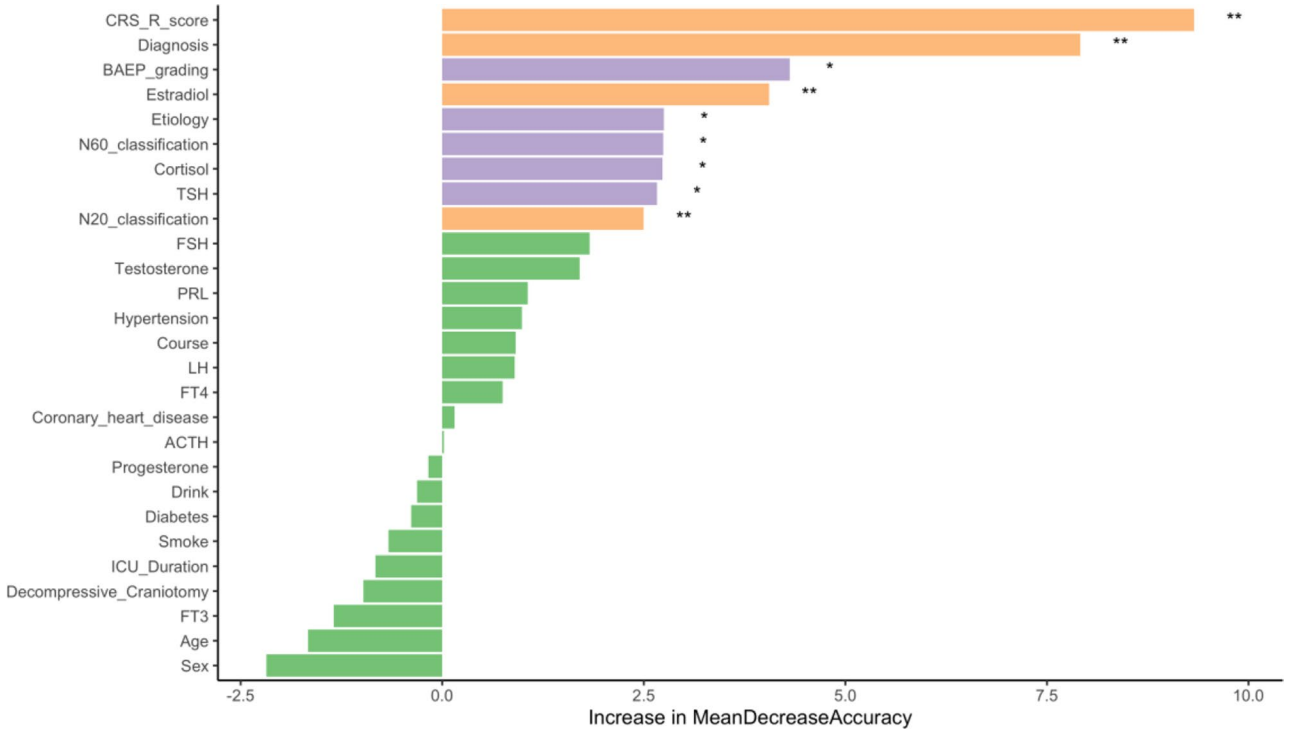

Fig. 2 Variable importance diagram of the random forest model

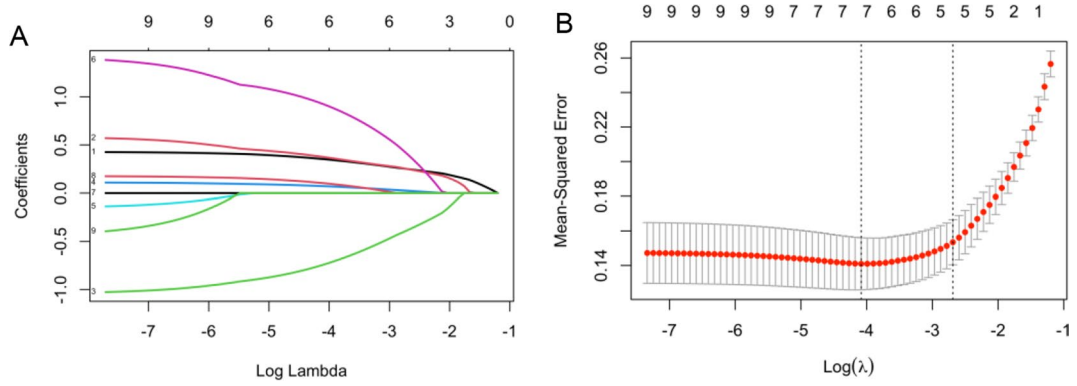

Fig. 3 **A** Lasso coefficient profiles of 9 alternative factors. **B** The tuning parameter λ (lambda) selection in the Lasso models used 10-fold cross validation by minimum criteria

Table 2 Multivariate logistic regression analysis

Variable	OR(95%CI)	*P*-Values
CRS-R score	1.05(1.02,1.08)	0.002
Diagnosis	1.13(0.91,1.41)	0.26
BAEP grading	0.88(0.79,0.98)	0.02
Estradiol	1.01(1.00,1.02)	0.01
N60 classification	1.22(1.01,1.48)	0.04
TSH	1.03(0.99,1.05)	0.07

OR, odd ratio; CI, confidence interval; coma recovery scale-revised, CRS-R

potentials, as a method for assessing brainstem conduction pathways, is one of the earliest clinical tools used to predict the prognosis of patients with disorders of consciousness.

While bilateral absence of N20 and BAEP wave V showed the highest specificity (100%, 95% CI: 85.9-100%) and positive predictive value (100%, 95% CI: 80.8-100%) for poor outcome in patients with severe ischemic brain injury [41]. Our study and previous study [42] support that BAEP grading is associated with the prognosis of DOC patients and can serve as an independent predictor for PDOC patients.

The halamic-cortical dysfunction is crucial in the pathophysiology of DOC patients. Median nerve SEPs, as one of the representatives reflecting the thalamocortical pathway, still have controversial predictive value in the prognosis of PDOC patients; in our study, the classification of N20 cannot be serve as an independent predictive

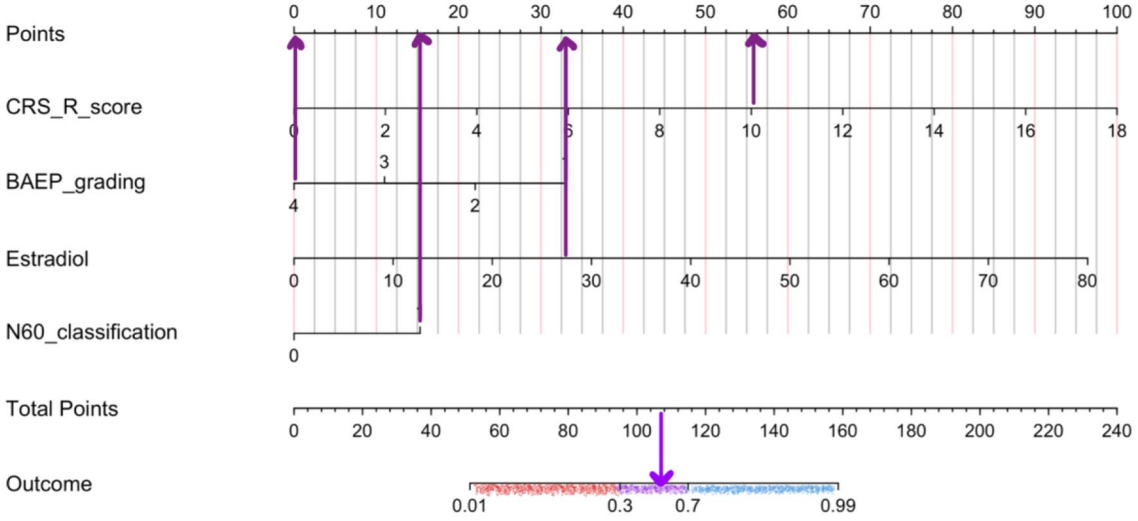

Fig. 4 A visual nomogram for predicting the improvement of consciousness in PDOC patients; for instance, the case indicated by the pink arrow, a CRS-R score of 10, BAEP grading of 4, N60 presence and an estradiol level of 28 pg/ml. Considering these four variables, the corresponding probability of regaining consciousness is 0.49

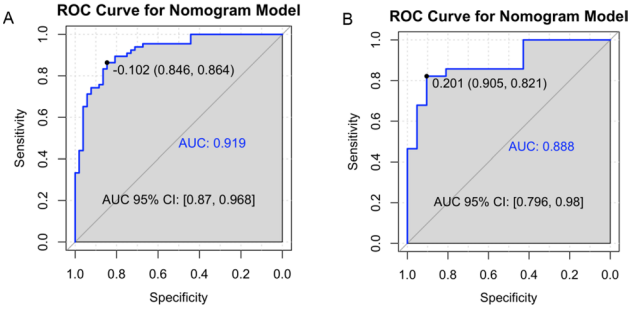

Fig. 5 **A** The ROC curves in the training set **B** The ROC curves in the validation set

factor for the prognosis of chronic disorders of consciousness, which is inconsistent with previous studies [43, 44]. Secondly, while short-latency potential measurements are effective in evaluating the integrity of sensory pathways and their corresponding cortical regions, they do not account for the secondary processing that occurs within higher-order cortical networks. The engagement of more distant cortical regions necessitates the intactness of these second-order networks, which in turn are responsible for the generation of medium and long-latency potentials [45].MLSEP are not only regulated by the ascending reticular activation system but are also correlated with cortical and subcortical functional connectivity integrity [12, 46]. They can reflect higher-order brain processes, which are essential for the recovery of consciousness and favorable outcomes after acquired brain injury. Previous studies have indicated that bilateral absence of the N60 component is associated with Previous studies suggest that the presence of N60/N70 responses may be a potential indicator of good prognosis [47–50], while the absence of N60 bilaterally indicates poor prognosispoor prognosis [12], with a false positive rate of 8% (95% CI 0.04–0.16) [51].However, these studies mainly focus on patients with early coma, and there is limited research on MLSEP in patients with PDOC.

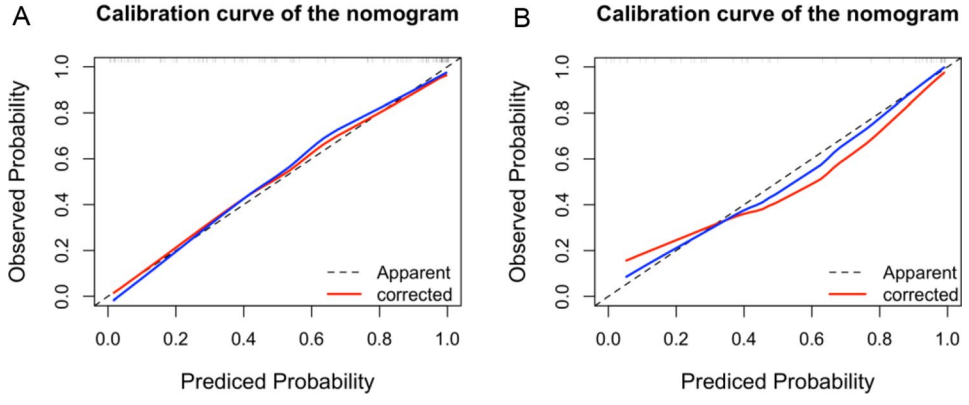

Fig. 6 **A** The calibration curve in the training set **B** The calibration curve in the validation set

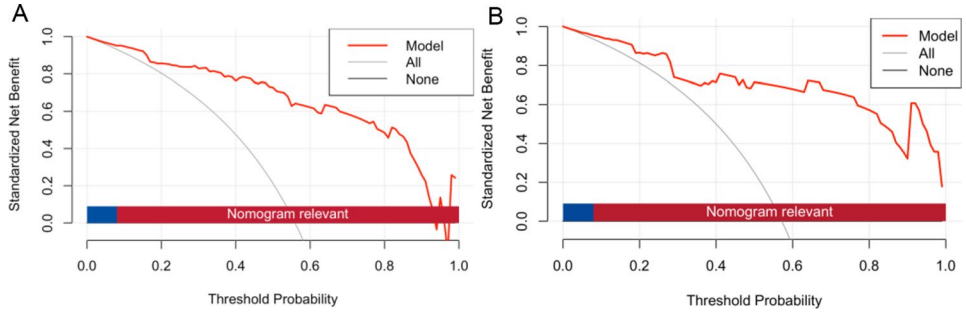

Fig. 7 **A** The decision curve in the training set **B** The decision curve in the validation set

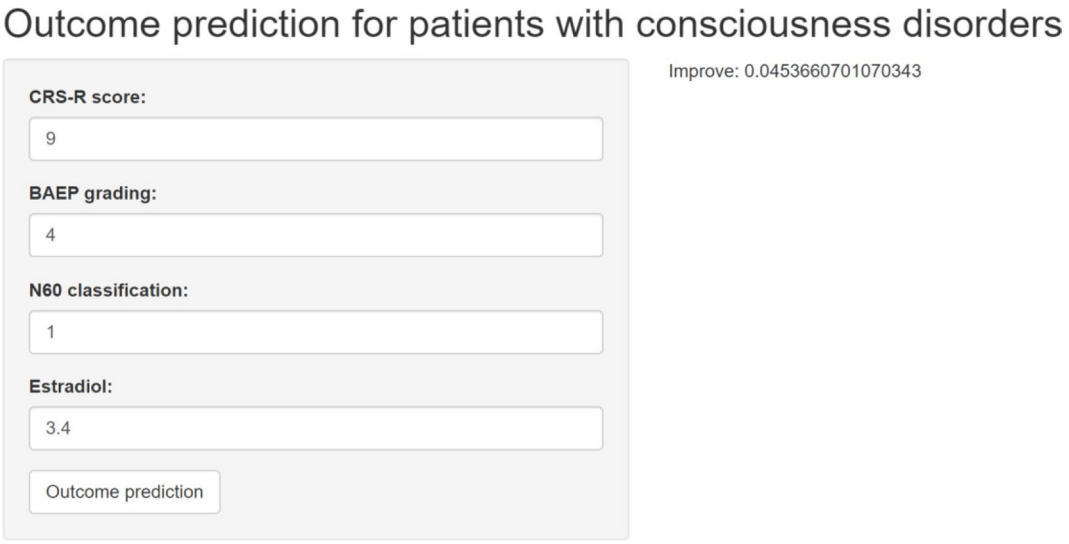

Fig. 8 Construction of a web-based calculator for predicting outcomes of prolonged disorders of consciousness based on the mode(https://outcome-prediction.shinyapps.io/outcome-prediction-1/)

In this study, we found that the presence of N60 was an independent predictor of the 6-month prognosis of PDOC, indicating better subcortical functional connectivity and a higher likelihood of consciousness recovery.

Pituitary dysfunction is a common complication after brain injuries [16–20]. Therefore, changes in the endocrine function of the hypothalamic-pituitary axis can be considered one of the initially measurable alterations after brain injury [51].Brain injury orcerebral edema can damage the anatomical structure of the hypothalamus, leading to a decrease in gonadal hormone level [52, 53]. Some studies have identified a deficiency in hypothalamic-pituitary-related hormones in patients with severe DOC [54, 55]. Our study revealed that estradiol levels were independent predictors of the prognosis of PDOC. Evidence suggests that estradiol has neuroprotective effects [56, 57]and can directly regulate cortical excitability and interhemispheric connectivity. In a comparative study investigating the efficacy of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) and sham stimulation of the left dorsolateral prefrontal cortex in patients with PDOC, researchers observed that responders to HF-rTMS treatment exhibited relatively high estradiol levels compared to non-responders. Based on these findings, HF-rTMS may potentially therapeutically impact PDOC by enhancing estradiol levels [58]. The aforementioned studies provide a theoretical basis for considering estradiol as a predictor of prognosis in patients with PDOC.

In our study, the combination of CRS-R score, BAEP grading, N60 classification and Estradiol was found to be a reliable predictor of the prognosis for patients with prolonged disorders of consciousness, with an AUC of 0.888 in the validation set.Liu and colleagues found that the combination of N60 and MMN within 7 days after coma had good predictive performance for arousal, with an AUC value of 0.852 [50].It's important to note that while the former model is primarily designed to predict patients in the acute phase, our study focuses on patients with PDOC. Additionally, our study incorporated behavioral assessment and estradiol levels alongside electrophysiological indicators, enhancing the prognostic value from various perspectives. Kang et al. conducted a study utilizing age, diagnosis, GCS score, and BAEP

grading, yielding an AUC of 0.815 in their retrospective prognostic model study [42]. This AUC was lower than that of our model (AUC = 0.888), possibly owing to the fact that compared to the GCS score, the CRS-R score is more suitable for the behavioral assessment of patients with PDOC. Secondly, N60 may provide information on higher-order cortical information processing capabilities.

Moreover, estradiol can serve as an objective indicator to reflect the serological changes in patients with PDOC and provide partial prognostic information.

In our study, several limitations should be acknowledged. First and foremost, it is important to acknowledge that our study, being a single-center investigation with a relatively small sample size, may not be fully representative of broader patient populations, thereby potentially limiting the generalizability of our findings. Moreover, the etiological distribution of our study cohort was not uniform, with stroke cases significantly outnumbering other etiologies. This uneven distribution could introduce a degree of bias in our analysis. Additionally, considering the complexity of our predictive model, which incorporates multiple variables, we recognize the necessity for validation in a larger and more diverse cohort to further substantiate our results and enhance the robustness of our conclusions.Future research endeavors should prioritize the implementation of dynamic monitoring of hormone levels, a strategy that holds the potential to significantly enhance the precision of patient classification and stratification in clinical management. It is imperative to recognize that neurophysiological data, often gathered within the complex signal-to-noise milieu of intensive care rehabilitation units, predominantly depend on visual analysis that is notably less reliable for interpreting evoked potential outcomes. Given these limitations, there is a pressing need to develop and deploy robust quantitative analytical methods or to harness the power of machine learning techniques. Such advancements could markedly improve the stability and reliability of research findings, thereby bolstering the overall validity and applicability of the results.

Conclusion

In conclusion, the nomogram model, which incorporates CRS-R score, BAEP grading, N60 classification and Estradiol, proves to be advantageous for assessing the short-term prognosis of patients with prolonged disorders of consciousness, with a high degree of accuracy. This model not only aids in prognostication for PDOC but also assists in refining treatment strategies and ensuring the judicious use of healthcare resources.

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Author contributions
JuanjuanFu and Hui Feng carried out the studies, participated in collecting data, and drafted the manuscript. Huaping Pan and Yongli Wu performed the statistical analysis and participated in its design. Fangyu Chen and Huiyue Feng participated in acquisition, analysis, or interpretation of data and draft the manuscript. Hongxing Wang was responsible for research supervision, guidance and fund acquisition. All authors read and approved the final manuscript.

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Data availability
The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request. Due to patient privacy concerns, raw data are not publicly available; however, de-identified data can be provided after execution of a data use agreement.

Declarations

Ethical approval
The study adhered to the Declaration of Helsinki II and good clinical practice guidelines, and was approved by the ethics committee of Jiangning Hospital Affiliated to Nanjing Medical University (Approval Code:2022-03-047-k01, Date:2023-02-22).

Consent to participate
Legal caregivers of all participants provided written informed consent.

Consent to publish
Not applicable.

Competing interests
The authors declare no competing interests.

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