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Analysis of Risk Factors and Development of a Prediction Model for Cognitive Dysfunction Associated with Pediatric Sepsis

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Abstract

Objective To investigate the risk factors for cognitive dysfunction in pediatric patients with sepsis, to develop a visualized risk prediction nomogram model, and to validate it. **Methods** A total of 206 pediatric patients with sepsis admitted to the PICU of Gansu Maternal and Child Health Hospital between January 2021 and December 2024 were enrolled as study subjects. Based on their Montreal Cognitive Assessment (MoCA) scores obtained 12 months after discharge, these patients were divided into a cognitive impairment group (n=78) and a normal cognition group (n=128). Using a stratified random sampling method at a ratio of 7:3, the patients were further subdivided into a training cohort (n=144) and a validation cohort (n=62).

The training cohort was used to identify risk factors for cognitive dysfunction and to establish a predictive model, while the validation cohort was used to evaluate the predictive performance of the model. Within the training cohort, differences in general clinical data and laboratory parameters between the two groups were analyzed and compared; LASSO regression was employed for variable selection; multivariate logistic regression analysis was conducted to identify independent risk factors; and a nomogram prediction model was constructed. The discriminative ability of the model was evaluated using the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC); the calibration performance was assessed using calibration curves and the Hosmer–Lemeshow test; and the Decision Curve Analysis (DCA) was used to evaluate the clinical utility of the model. Internal validation was subsequently performed on the validation cohort. **Results** Among the 206 pediatric patients, 78 cases (37.86%) developed cognitive dysfunction. In the training cohort, statistically significant differences were observed between the two groups of pediatric patients regarding duration of mechanical ventilation, admission PCIS score, proportion of patients with septic shock, NE%, CRP, PCT, D-dimer, Lac, CK, Cys-C, Cr, Glu, and Ca levels ($P < 0.05$). Multivariate logistic regression analysis revealed that septic shock (OR=3.267, 95% CI: 1.611–6.625), CRP (OR=1.006, 95% CI: 1.003 – 1.009), Lac (OR=1.135, 95% CI: 1.001–1.287), Cys-C (OR=2.006, 95% CI: 1.287–3.128), and Glu (OR=1.234, 95% CI: 1.087–1.400) were independent risk factors for cognitive dysfunction in pediatric patients with sepsis. The nomogram model constructed based on these factors demonstrated AUC values of 0.810 in the training cohort and 0.795 in the validation cohort. The Hosmer–Lemeshow goodness-of-fit test results indicated good model performance. with $P = 0.973$ in the training cohort and $P = 0.843$ in the validation cohort. The DCA curve showed that the model exhibited favorable clinical net benefit within the probability threshold range of 0.1–0.9. **Conclusion** Septic shock, CRP, Lac,

Cys-C and Glu are independent risk factors for cognitive dysfunction in pediatric patients with sepsis. The nomogram prediction model developed based on these factors demonstrates excellent discriminative ability, calibration, and clinical utility.

Keywords: sepsis; pediatrics; cognitive impairment; risk factors; nomogram; predictive model

Sepsis is one of the leading causes of childhood mortality and disability worldwide, with approximately 1.2 million children infected annually [1]. Although survival rates for pediatric sepsis have significantly improved due to advances in critical care, current clinical practices remain insufficiently focused on long-term neurocognitive impairments—disabling sequelae that severely affect quality of life[2]. These cognitive deficits, including attentional deficits, memory impairment, and language comprehension difficulties, may persist or even worsen for months after recovery from sepsis[3]. In China, research on long-term cognitive outcomes following sepsis has largely concentrated on adult populations or analyzed single risk factors, leaving a critical gap in clinical tools capable of early, individualized identification of high-risk children[4]. Therefore, developing a child-specific predictive model integrating key risk factors for cognitive dysfunction holds significant clinical importance and urgency. This study systematically identifies independent risk factors associated with long-term cognitive impairment in pediatric sepsis patients and constructs an individualized risk prediction nomogram model, aiming to provide evidence-based support for early identification of at-risk children and optimization of clinical management strategies.

1 Object and Methods

1.1 Research Subject

Retrospective analysis of clinical data from children with sepsis admitted to Gansu Provincial Maternity and Child Health Hospital between January 2021 and December 2024. Inclusion criteria: age 4–14 years; meeting the diagnostic criteria for Sepsis 3.0[5] according to

the 2016 International Consensus on Sepsis, defined as infection plus a pediatric Sequential Organ Failure Assessment (pSOFA) score ≥2 points as proposed by Matics TJ[6] et al;first admission to our PICU due to sepsis with hospitalization duration ≥48 hours; completion of cognitive function assessment at 12 months post-discharge. Exclusion criteria: history of confirmed central nervous system disorders or neurodevelopmental delay; presence of severe congenital heart disease, inborn metabolic disorders, or chromosomal abnormalities; concurrent advanced malignancy or other end-stage diseases with an expected survival time of less than 6 months; or significant missing clinical data or follow-up assessment information.

1.2 Cognitive Function Assessment and Grouping Method

This study used the Montreal Cognitive Assessment (MoCA)[7] as the cognitive function evaluation tool. The total MoCA score is 30 points, with a score of ≥26 indicating normal cognition; scores between 18 and 25 suggest mild cognitive impairment; and scores ≤17 indicate moderate to severe cognitive impairment. Cognitive function assessments were uniformly conducted at the 12-month follow-up after discharge from the hospital. Using stratified random sampling, the 206 participants were randomly divided into a training cohort (*n=144) and a validation cohort (n*=62) in a 7:3 ratio.

1.3 Collecting Data

1.3.1 General Information

Gender, age, BMI, temperature, heart rate, blood pressure, nutritional status, comorbidities, length of hospital stay, ICU duration, mechanical ventilation time, use of vasopressors, antibiotic administration within 1 hour, septic shock status, and Pediatric Critical Illness Score (PCIS) upon admission.

1.3.2 Laboratory examination indicators

① Complete blood count: white blood cell count (WBC), platelet count (PLT), neutrophil

percentage (NE%), lymphocyte percentage (LY%), hemoglobin (Hb); ② Inflammatory markers: C-reactive protein (CRP), procalcitonin (PCT); ③ Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (Fib), D-dimer (D-Dimer); ④ Blood gas analysis: pH, base excess (BE), blood lactate (Lac); ⑤ Electrolytes: sodium (Na), potassium (K), calcium (Ca), inorganic phosphorus (P); ⑥ Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB); ⑦ Renal function: blood urea nitrogen (BUN), creatinine (Cr), cystatin C (Cys-C); ⑧ Cardiac enzyme panel: creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB); ⑨ Metabolic indicators: blood glucose (Glu), triglycerides (TG), total cholesterol (TC); ⑩ Immunoglobulins: immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM).

1.4 Statistical Analysis

Data analysis was performed using the R language and SPSS 26.0 statistical software. Continuous variables following a normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$), and comparisons between two groups were conducted using independent sample t-tests. For continuous variables not normally distributed, data were presented as median and interquartile range [M (P25, P75)], and group comparisons were analyzed using the Mann-Whitney U rank-sum test. Categorical variables were expressed as frequency and percentage [n (%)], and comparisons between groups were performed using Pearson's chi-square test or Fisher's exact probability method. The dataset was divided into training and validation cohorts using a 7:3 stratified sampling approach. In the training cohort, variables with $P < 0.05$ in univariate logistic regression were included in multivariate logistic regression analysis; additionally, LASSO (Least Absolute Shrinkage and Selection Operator) regression was applied to further validate the model and address multicollinearity issues. Model fit was

assessed using the Hosmer-Lemeshow test, predictive performance was evaluated via receiver operating characteristic (ROC) curves, and the clinical net benefit of the model at different threshold probabilities was assessed using decision curve analysis (DCA)[8] .

All statistical tests were performed using two-tailed tests with a significance level of $\alpha = 0.05$, and *differences* were considered statistically significant when $P < 0.05$.

2 Results

2.1 Follow-up Results

A total of 206 pediatric sepsis patients completed the MoCA cognitive assessment and were included in the final analysis during the 12-month follow-up after discharge. Based on the cutoff criteria, 78 patients (37.86%) were classified into the cognitive impairment group, while 128 (62.14%) were assigned to the normal group. Using stratified random sampling, the 206 participants were randomly divided into a training cohort (*n*=144, including 55 from the cognitive impairment group and 89 from the normal group) and a validation cohort (*n*=62, including 23 from the cognitive impairment group and 39 from the normal group) in a 7:3 ratio.

2.2 Comparison of Baseline Characteristics between Training and Validation Cohorts

The two cohorts showed no significant differences in all baseline variables and outcome incidence listed in Table 1 ($P > 0.05$), indicating good comparability. Additionally, there was no significant difference in the incidence of cognitive impairment between the two cohorts ($P = 0.879$), confirming their strong comparability. Thus, the training cohort and validation cohort are suitable for model development and independent validation, respectively (see Table 1 for details).

Table 1 Comparison of baseline characteristics between the training and validation cohorts

Variable	Training cohort (n=144)	Validation cohort (n=62)	χ^2 /Z/t	P
Male/n (%)	92 (63.89)	40(64.52)	0.008	0.930
Age / years	8.00 (7.00, 9.00)	8.00 (6.75, 9.00)	0.215	0.830
BMI/(kg/m^2)	14.60 (12.83, 16.00)	14.65 (12.80, 16.05)	0.142	0.887
Malnutrition/n (%)	40 (27.78)	17(27.42)	0.003	0.957
Underlying disease/n (%)	23(15.97)	9(14.52)	0.072	0.789
Length of hospital stay / days	21.00 (12.00, 32.00)	20.50 (13.00, 31.25)	0.182	0.856
ICU days	13:00 (7:00, 21:00)	12.50 (7.75, 21.25)	0.105	0.917
Mechanical ventilation duration/h	72.50 (10.00, 160.00)	70.00 (8.50, 155.00)	0.378	0.706
Vasopressor use/n (%)	77(53.47)	33(53.23)	0.001	0.974
Antibiotic use within 1 hour / n (%)	88(61.11)	38(61.29)	0.001	0.980
Septic shock/n (%)	75(52.08)	32(51.61)	0.004	0.950
PCIS/Entry	79.00 (74.00, 84.00)	79.50 (74.75, 84.25)	0.265	0.791
Cognitive impairment/n (%)	55(38.19)	23(37.10)	0.023	0.879
WBC/($\times 10^9$/L)	10.30 (5.85, 17.00)	10.45 (5.90, 16.95)	0.108	0.914
NE%	69.50 (54.20, 83.10)	68.80 (53.50, 82.50)	0.198	0.843
CRP/(mg/L)	80.50 (22.50, 205.00)	78.50 (21.00, 198.00)	0.165	0.869
PCT/(ng/mL)	18.20 (3.50, 48.50)	17.85 (3.20, 46.50)	0.142	0.887

D-Dimer/(mg/L)	5.50 (1.65, 12.50)	5.40 (1.55, 12.00)	0.221	0.825
Lac/(mmol/L)	2.45 (1.45, 4.65)	2.40 (1.40, 4.50)	0.176	0.860
Cys-C/(mg/L)	1.20 (0.88, 1.75)	1.22 (0.85, 1.72)	0.092	0.927
Cr/(μ mol/L)	35.00 (22.00, 58.00)	34.50 (22.75, 56.50)	0.108	0.914
Glu/(mmol/L)	5.20 (3.75, 6.65)	5.18 (3.70, 6.60)	0.135	0.893

2.3 Comparison of General Clinical Data between the Two Groups of Children in the Training Cohort

There were no statistically significant differences between the two groups in terms of gender, age, BMI, temperature, heart rate, blood pressure, nutritional status, distribution of underlying diseases, length of hospital stay, ICU stay, use of vasopressors, or antibiotic administration within one hour ($P > 0.05$).

There were significant statistical differences between the two groups in terms of disease severity indicators, including duration of mechanical ventilation, proportion of septic shock, and initial PCIS scores upon admission ($P < 0.001$)(see Table 2 for details).

Table 2 Comparison of general clinical data between the two groups of children in the training cohort

Variable	Normal group (n=89)	Cognitive impairment group (n=55)	χ^2 /Z/t	P
Male/n (%)	60 (67.42)	32(58.18)	1.246	0.264
Age / years	8.00 (7.00, 9.00)	8.00 (6.00, 9.00)	0.045	0.964
BMI/(kg/m^2)	14.70 (12.85, 16.10)	14.50 (12.80, 15.85)	0.398	0.691
Body Temperature / $^\circ$C	37.83±1.05	38.12±1.25	1.485	0.140
Heart rate (beats per	152.00 (130.00,	161.00 (138.00, 178.00)	0.762	0.446

minute)	171.50)			
Systolic blood pressure/mmHg	90.05±17.12	92.85±21.60	0.852	0.396
Diastolic blood pressure/mmHg	57.30±15.20	57.10±15.50	0.075	0.940
Malnutrition/n (%)	26(29.21)	14 (25.45)	0.236	0.627
Underlying disease/n (%)	14(15.73)	9(16.36)	0.011	0.917
Length of hospital stay / days	20.00 (12.00, 30.00)	23.00 (13.00, 37.00)	1.105	0.269
ICU days	12:00 (7:00, 21:00)	15.00 (8.00, 23.50)	1.182	0.237
Mechanical ventilation duration/h	44.50 (0.00, 140.20)	115.20 (66.50, 180.30)	3.518	<0.001
Vasopressor use/n (%)	44 (49.44)	33 (60.00)	1.532	0.216
Antibiotic use within 1 hour / n (%)	53 (59.55)	35 (63.64)	0.241	0.624
Septic shock/n (%)	35 (39.33)	40 (72.73)	15.482	<0.001
PCIS/Entry	81.00 (76.00, 86.00)	76.00 (71.00, 80.00)	3.402	<0.001

2.4 Comparison of laboratory examination indicators between the two groups of children in the training cohort

There were statistically significant differences between the two groups in NE% (P=0.037), CRP (*P=0.002), PCT (P*=0.004), D-Dimer (P=0.002), Lac (P=0.006), Ca (P=0.043), CK (P=0.037), Cys-C (P=0.014), Cr (P=0.013), and Glu (P=0.009). However, no significant

differences were observed between the groups in WBC, PLT, LY%, Hb, APTT, PT, Fib, pH, BE, Na, K, P, CK-MB, ALT, AST, TBIL, ALB, BUN, TG, TC, or immunoglobulin levels (IgG, IgA, IgM) ($P > 0.05$)(see Table 3 for details).

Table 3 Comparison of laboratory examination indicators between the two groups of children in the training cohort

Variable	Normal group (n=89)	Cognitive impairment group (n=55)	Z/t	P
Complete Blood Count				
WBC/($\times 10^9$/L)	10.25 (5.95, 16.85)	10.65 (5.30, 17.50)	0.385	0.700
PLT/($\times 10^9$/L)	175.00 (70.00, 320.00)	153.00 (46.00, 282.00)	1.205	0.228
NE%	66.50 (48.50, 81.70)	74.20 (59.80, 85.90)	2.085	0.037
LY%	2.12 (0.78, 3.50)	2.20 (0.80, 3.75)	0.245	0.806
Hb/(g/L)	105.00 (91.00, 119.00)	101.00 (89.00, 124.00)	0.382	0.702
Inflammatory markers				
CRP/(mg/L)	50.10 (14.00, 171.50)	143.20 (40.50, 275.80)	3.142	0.002
PCT/(ng/mL)	10.20 (1.45, 30.50)	31.85 (7.80, 63.00)	2.875	0.004
Coagulation function				
APTT/S	42.00 (32.85, 63.50)	41.50 (32.00, 61.50)	0.165	0.869
PT/S	14.92 (12.80, 21.50)	15.55 (13.60, 20.30)	0.702	0.483
Fib/(g/L)	2.92 (1.75, 4.45)	3.30 (2.00, 4.72)	0.745	0.456

D-Dimer/(mg/L)	4.20 (1.05, 8.40)	8.15 (2.70, 22.50)	3.085	0.002
Blood gas parameters				
pH value	7.40 (7.31, 7.46)	7.35 (7.25, 7.43)	1.425	0.154
BE/(mmol/L)	-6.70 (-11.10, -3.30)	-8.85 (-12.15, -4.10)	1.535	0.125
Lac/(mmol/L)	2.20 (1.20, 4.20)	2.85 (1.85, 5.45)	2.752	0.006
Electrolyte indicators				
Na/(mmol/L)	135.00 (131.00, 138.00)	135.90 (130.00, 138.80)	0.252	0.801
K/(mmol/L)	4.12 (3.68, 4.80)	3.98 (3.34, 4.50)	1.642	0.101
P/(mmol/L)	1.42 (1.00, 1.98)	1.39 (1.04, 2.10)	0.122	0.903
Ca/(mmol/L)	2.15 (1.98, 2.35)	2.08 (1.78, 2.25)	2.025	0.043
Liver function				
ALT/(U/L)	24.50 (15.85, 69.00)	40.50 (19.50, 122.50)	0.812	0.417
AST/(U/L)	51.50 (30.50, 163.50)	81.50 (39.00, 231.00)	1.612	0.107
TBIL/(μ mol/L)	11:30 (7:45, 20:45)	9.30 (6.10, 15.95)	1.245	0.213
ALB/(g/L)	35.30 (30.45, 39.10)	34.30 (30.20, 40.20)	0.365	0.715
Cardiac enzyme panel				
CK/(U/L)	148.20 (58.00, 628.50)	378.50 (95.00, 1485.00)	2.082	0.037
CK-MB/(U/L)	62.70 (29.80, 280.30)	78.00 (43.50, 306.00)	0.562	0.574
renal function				

Cys-C/(mg/L)	1.12 (0.83, 1.52)	1.42 (0.95, 2.12)	2.452	0.014
BUN/(mmol/L)	5.15 (3.70, 8.50)	5.85 (4.00, 13.05)	1.575	0.115
Cr/(μ mol/L)	31.00 (21.00, 49.00)	42.50 (25.00, 84.00)	2.478	0.013
Metabolic indicators				
Glu/(mmol/L)	5.00 (3.60, 6.10)	5.70 (4.00, 7.60)	2.612	0.009
TG/(mmol/L)	1.10 (0.75, 1.65)	1.30 (0.70, 1.93)	0.628	0.530
TC/(mmol/L)	2.45 (1.76, 3.20)	2.34 (1.74, 2.88)	0.752	0.452
Immune indicators				
IgG/(g/L)	5.55 (3.34, 7.80)	4.84 (3.02, 7.65)	0.358	0.720
IgA/(g/L)	0.50 (0.24, 0.80)	0.50 (0.24, 0.93)	0.475	0.635
IgM/(g/L)	0.64 (0.40, 0.99)	0.69 (0.46, 1.00)	0.792	0.428

In summary, a univariate analysis of the training cohort identified 13 candidate variables with statistically significant differences, including three general clinical indicators (duration of mechanical ventilation, septic shock, and PCIS score upon admission) and ten laboratory indicators (NE%, CRP, PCT, D-dimer, Lac, Ca, CK, Cys-C, Cr, Glu).

2.5 LASSO Regression Variable Selection Results

The 13 candidate variables identified as statistically significant in the univariate analysis of the training cohort were included in a LASSO regression model for further feature selection. Through tenfold cross-validation, six variables were retained as key features: duration of mechanical ventilation, septic shock, CRP, lactate, cystatin C, and glucose (Figure 1).

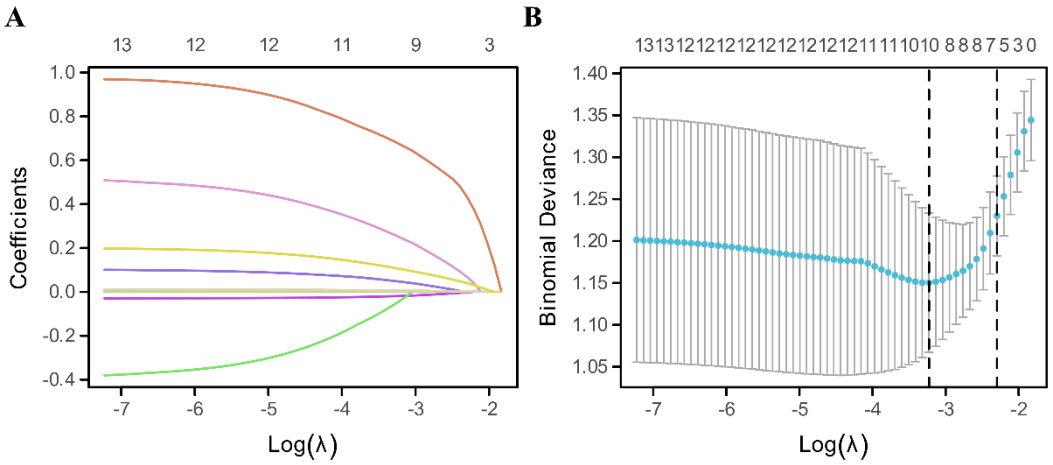


Figure 1 Feature selection using LASSO regression

(A) LASSO regression coefficient trajectory plot; (B) tenfold cross-validation curve

2.6 Multivariate Logistic Regression Analysis and Nomogram Model Construction

In the training cohort, a multivariate logistic regression prediction model was constructed using six key variables selected by LASSO regression as independent variables, with cognitive dysfunction in septic pediatric patients (0 = no, 1 = yes) as the dependent variable. The results of the regression analysis are shown in Table 4.

Table 4 Multivariate Logistic Regression Analysis of Factors Influencing Cognitive Dysfunction in Pediatric Sepsis Patients

Variable	β	S.E	Z	P	OR (95% CI)
Septic shock	1.184	0.361	3.283	0.001	3.267 (1.611-6.625)
Lac	0.126	0.064	1.971	0.049	1.135 (1.001-1.287)
CRP	0.006	0.002	3.710	<0.001	1.006 (1.003-1.009)
Cys-C	0.696	0.227	3.072	0.002	2.006 (1.287-3.128)
Glu	0.210	0.064	3.260	0.001	1.234 (1.087-1.400)

Duration of mechanical ventilation	0.052	0.038	1.368	0.171	1.053 (0.977–1.135)

The results showed that for mechanical ventilation duration, the odds ratio *(OR)* was 1.053, with a 95% confidence interval (CI) of 0.977–1.135, indicating a weak positive trend between mechanical ventilation duration and the risk of cognitive impairment; however, P = 0.171 > 0.05. After adjusting for septic shock, it did not have independent predictive value and was thus excluded in stepwise regression to achieve a more parsimonious model. Septic shock, CRP, lactate, cystatin C, and glucose were identified as independent risk factors for cognitive dysfunction in pediatric sepsis patients. Based on these five independent risk factors, a nomogram prediction model was constructed using the rms package in R (Figure 2).

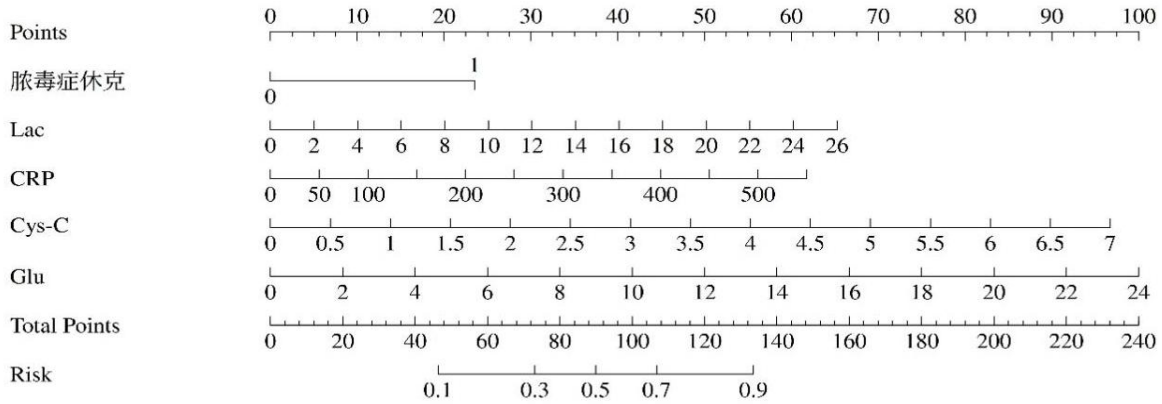


Figure 2 Nomogram prediction model

2.7 Evaluation of Predictive Model Performance

2.7.1 Model Discrimination Evaluation

ROC curve analysis showed that the nomogram model had AUCs of 0.810 (95% *CI: 0.749–0.872) and 0.795 (95% CI*: 0.683–0.907) for predicting cognitive dysfunction in pediatric sepsis patients in the training and validation cohorts, respectively. The corresponding sensitivities at the optimal cutoff were 76.4% and 73.9%, and specificities were 75.3% and 74.4%, indicating good discriminatory performance in the training cohort and strong stability and reproducibility in the validation cohort (Figure 3A, Figure 4A).

2.7.2 Model Calibration Evaluation

The Hosmer-Lemeshow goodness-of-fit test yielded χ^2=2.225, *P*=0.973 in the training cohort and χ^2=4.156, *P*=0.843 in the validation cohort, indicating no significant difference between the predicted probabilities and observed probabilities. This confirms that the model demonstrates good calibration performance in both the training and validation cohorts (Figure 3B, Figure 4B).

2.7.3 Evaluation of Model Clinical Practicality

The DCA curve results indicate that the model has good clinical utility in the training cohort across a threshold probability range of 0.1 to 0.9, and in the validation cohort, the model provides positive net clinical benefit within the threshold probability range of 0.1 to 0.85, confirming its clinical applicability (Figure 3C, Figure 4C).

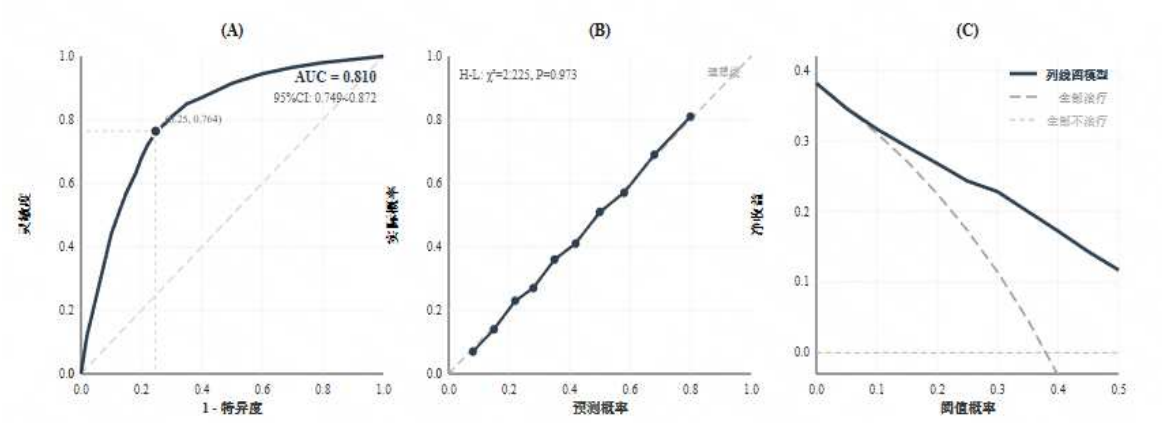


Figure 3 Validation of the predictive model's performance in the training cohort

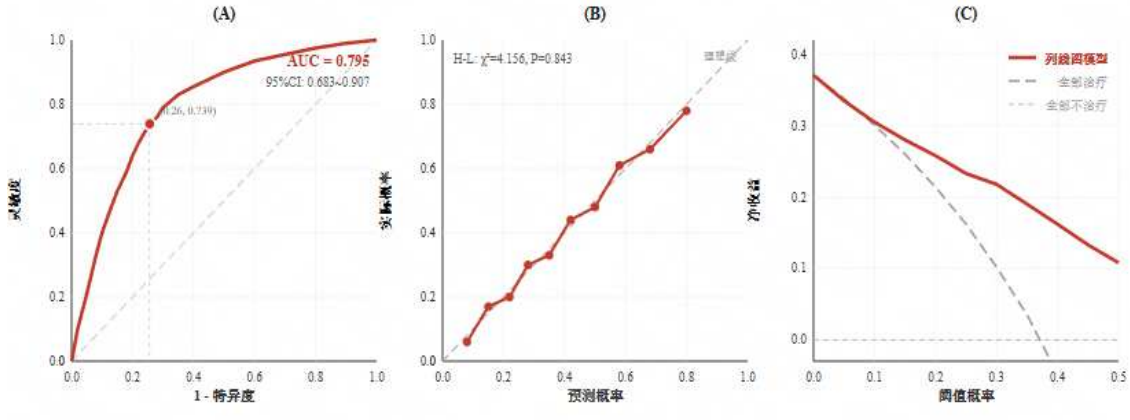


Figure 4 Internal validation of the prediction model in the validation cohort

The nomogram prediction model developed in this study demonstrated good discrimination, calibration, and clinical utility in both independent validation cohorts, indicating strong stability and clinical applicability.

Discussion

The incidence of central nervous system complications in children with sepsis can reach up to 70%. Inflammatory cytokine storms, impaired microcirculatory perfusion, disruption of the blood-brain barrier, and secondary metabolic disturbances can lead to neuronal and structural brain damage[9-11], resulting in impairments in cognition, language, attention, and other functions[2]. Identifying high-risk factors for cognitive dysfunction and establishing predictive models hold significant value for clinical diagnosis, treatment, and long-term intervention.

This study identified five independent risk factors that form the "low perfusion-inflammation-metabolism" vicious triangle of sepsis-related brain injury: septic shock and elevated lactate levels indicate cerebral hypoperfusion and hypoxic damage; CRP reflects systemic inflammation and blood-brain barrier disruption; hyperglycemia indicates stress-induced metabolic disturbances, while elevated cystatin C suggests early renal injury—both of which exacerbate neurotoxicity through oxidative stress and toxin

accumulation. A 12-month follow-up of 206 pediatric sepsis patients showed a cognitive impairment rate of 37.86%, indicating that this long-term adverse outcome is common in pediatric critical care, consistent with previous prospective studies[12] .

Univariate analysis showed that children in the cognitive impairment group had more severe disease, stronger inflammatory responses, and greater organ damage, consistent with the patterns observed in adult septic encephalopathy[13]. Septic shock was identified as a significant independent risk factor, and the resulting cerebral hypoperfusion was found to be a key mechanism of cognitive injury[14], aligning with conclusions from Zhang[15] et al. Lactate, as a biochemical marker of tissue hypoxia and microcirculatory dysfunction, can cross the blood-brain barrier and mediate brain acidosis and neuroinflammation[16-17]; animal studies have also confirmed that reducing lactate levels improves cognitive deficits[18]. Elevated CRP drives disruption of the blood-brain barrier and activates microglia, leading to neuronal and synaptic damage[19-20],findings consistent with previous international pediatric research[21]. CysC is a sensitive marker of renal injury, and impaired kidney function may exacerbate brain damage and increase the risk of permanent cognitive impairment[22-23]. Although renal function indicators are rarely included in predictive models for this condition, this study provides additional supporting evidence. Stress-induced hyperglycemia worsens brain injury through oxidative stress and disruption of the blood-brain barrier[24, 25],multiple studies have confirmed that hyperglycemia is an independent risk factor for early cognitive impairment in sepsis[15, 26]. LASSO regression suggested that duration of mechanical ventilation has potential predictive value, but it did not enter the final model after adjustment for covariates. Prolonged mechanical ventilation typically indicates critical illness and recurrent hypoxemia, which are closely related to cerebral perfusion status[27]. Its effects may be explained by severe conditions such as septic shock, yet it remains clinically relevant and warrants further attention.

The nomogram prediction model constructed based on the above five independent risk

factors demonstrated good calibration in both the training and validation cohorts, as indicated by Hosmer-Lemeshow tests (P=0.973 and P=0.843). The DCA curve showed stable clinical net benefit across a wide range of threshold probabilities, with overall performance comparable to existing models for predicting cognitive impairment in adult sepsis[28] .Clinicians can collect these five indicators before a child's transfer out of the PICU or discharge and quickly calculate the long-term risk probability of cognitive impairment using the nomogram. For high-risk patients (e.g., those with a risk >80%), a stratified follow-up strategy should be implemented—such as advancing the first follow-up visit from 12 months post-discharge to 6 months—and, when necessary, incorporating cranial imaging or detailed neuropsychological assessments like the WISC to enable early warning and individualized intervention.

It should be noted that Lac, CRP, and Glu included in this model are dynamic fluctuating indicators. This study used the initial or worst values upon admission to construct the model, which can only reflect the patient's condition at a specific time point during the acute phase of critical illness, making it difficult to capture the dynamic changes of these markers throughout the course of sepsis. Predicting outcomes based on single cross-sectional measurements inherently has limitations. The predictive value of longitudinal changes in these markers for long-term cognitive outcomes requires further validation through prospective longitudinal studies.

In summary, this study confirms that septic shock, elevated lactate (Lac), elevated C-reactive protein (CRP), elevated cystatin C (Cys-C), and elevated glucose (Glu) are independent risk factors for cognitive dysfunction in pediatric sepsis patients. The nomogram model constructed based on these indicators demonstrates good predictive performance and clinical applicability, offering a quantitative tool for early identification of high-risk children.

This study, based on real clinical data from pediatric sepsis patients, identified independent risk factors for cognitive dysfunction and developed and validated a visual predictive model.

By employing multivariate regression to select core clinical indicators and constructing a nomogram model, this research quantifies the independent predictive value of each risk factor, overcoming the limitations of previous single-correlation analyses and advancing the field from risk factor screening to personalized risk prediction. Compared with adult sepsis cognitive outcome models, this study better aligns with the unique physiological characteristics of children—immature brain development, rapid disease progression, and distinctive compensatory mechanisms—thereby avoiding the adaptation issues associated with applying adult models to pediatric populations, resulting in greater clinical relevance and applicability. Moreover, all model parameters are routinely monitored in PICUs, making it suitable for widespread implementation across pediatric intensive care units and primary healthcare institutions. The model supports early screening, dynamic assessment, and stratified management of cognitive impairment in septic children, holding significant clinical value and public health implications for reducing long-term neurological disability and improving patient outcomes.

This study has several limitations. First, it is a single-center retrospective analysis with data from a single source, which may introduce selection and information bias. The lack of external validation through multicenter, large-sample datasets limits the model's generalizability and applicability. As such, the findings reflect only the clinical features of pediatric patients in this region and cannot be easily generalized to children from different geographical areas, varying levels of medical care, or diverse ethnic backgrounds. Second, cognitive function was assessed at fixed time points after discharge without long-term dynamic longitudinal follow-up, making it difficult to accurately capture the dynamic changes in cognitive function over time. This approach also hinders differentiation between reversible neurological abnormalities during the acute phase and persistent long-term cognitive impairments, potentially leading to biased

outcome assessments. Moreover, confounding factors such as baseline cognitive status upon admission, family history of neurodevelopmental disorders, home environment, and long-term rehabilitation interventions were not included, thus failing to fully account for individual baseline differences and environmental influences on prognosis. Third, the model underwent only internal validation and lacks external prospective validation across multiple centers; its stability, accuracy, and clinical utility require further evaluation. Fourth, the study focused solely on macro-level clinical risk factors without delving into micro-level pathological mechanisms such as inflammatory regulation, blood-brain barrier injury, and neuronal apoptosis, thereby failing to elucidate the molecular pathways underlying these risk factors and lacking in-depth mechanistic insights. Additionally, the study did not perform stratified analyses based on age groups or sepsis subtypes, nor did it adequately consider the heterogeneity of neurodevelopment in children, leaving room for improvement in model precision.

To address the aforementioned limitations, a multicenter, prospective cohort study will be conducted to increase sample size by including cases from multiple regions and hospitals at various levels, thereby enhancing external validation and improving the model's generalizability and stability. The follow-up period will be extended to establish a long-term dynamic monitoring system for precise assessment of children's long-term cognitive outcomes, with additional adjustment for confounding variables such as genetics, environmental factors, and baseline cognition to refine the risk factor evaluation framework. Furthermore, future research will integrate imaging and molecular biology indicators to optimize the model across clinical, radiological, and molecular mechanisms, thereby improving predictive performance and providing more robust theoretical and clinical support for early, precise prevention and control, mechanistic exploration, and targeted interventions in pediatric sepsis-related cognitive dysfunction.

Declarations ：

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the Ethics Committee of Gansu Provincial Maternity and Child Health Hospital (Gansu Provincial Central Hospital) (approval No.（2026）GSFY[069]). Written informed consent was obtained from the legal guardians (parents) of all enrolled children. Written assent was obtained from children aged ⩾ 8 years after age-appropriate explanation of the study.

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