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Original Article

Influencing factors and construction of a predictive model for neurodevelopmental outcomes in preterm low birth weight infants

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Abstract: Objective: To identify risk factors for adverse neurodevelopmental outcomes (ANO) in preterm low birth weight (PLBW) infants and to develop a predictive model. Methods: A retrospective analysis was conducted on 146 PLBW infants who underwent neurodevelopmental assessment at the Women and Children's Hospital of Ningbo University between August 2022 and August 2024. Neurodevelopmental status was evaluated using the Bayley Scales of Infant Development at a corrected age of two years. Infants were classified into either a normal neurodevelopmental outcome (NNO, n=85) group or an ANO group (n=61), according to their Bayley Mental Index scores. Data collected included demographic information, maternal health data, neonatal cranial ultrasound findings, and neonatal complications. Multivariate logistic regression was used to identify significant predictors, and receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of the model. Results: There were no significant differences in baseline demographic factors such as gestational age or birth weight between the two groups (all P>0.05). However, the ANO group exhibited a significantly higher incidence of hemorrhagic and ischemic cerebral lesions, bronchopulmonary dysplasia, and required longer durations of mechanical ventilation and oxygen therapy (all P<0.05). Multivariate logistic regression confirmed these factors as independent predictors of ANO. The composite predictive model, incorporating these variables, achieved an area under the AUC of 0.833, indicating good predictive accuracy. Validation with an external sample of 71 infants yielded an AUC of 0.854, demonstrating good agreement between predicted and observed outcomes. Conclusion: Cerebral lesions and respiratory complications were significant predictors of adverse neurodevelopmental outcomes in PLBW infants. The developed predictive model may support early identification of high-risk infants and facilitate timely interventions to improve long-term neurodevelopmental outcomes.

Keywords: Preterm infants, low birth weight, neurodevelopmental outcomes, predictive model, risk factors, Bayley scales of infant development

Introduction

Preterm low birth weight (PLBW) infants, defined as those born before 37 weeks of gestation and weighing less than 2,500 grams, account for approximately 17% of the global annual 15 million preterm births and represent a significant proportion of the neonatal population [1]. This subgroup is at increased risk for numerous complications, notably impaired neurodevelopmental outcomes [2]. The combined effect of prematurity and the inherent vulnerability associated with low birth weight predisposes these infants to neurological deficits such as cerebral palsy, cognitive delays, and sensory impairments, posing a major public health challenge [3]. Although advances in neonatal care have substantially improved the survival rates of PLBW infants, these gains have not consistently translated into better long-term neurodevelopmental outcomes [4, 5]. Therefore, understanding the factors influencing these outcomes is essential for developing effective preventive strategies and targeted interventions.

The neurodevelopment of preterm infants is shaped by multiple factors spanning the prenatal, perinatal, and postnatal periods [6-8].

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Prenatal influences include maternal health status, nutritional conditions, and socioeconomic factors, all of which critically affect the fetal environment [9]. During the perinatal period, the degree of prematurity and complications such as birth asphyxia, intraventricular hemorrhage, and sepsis are key determinants of neurodevelopmental outcomes [10]. Postnatally, factors such as nutritional status, infections, and the level of neonatal intensive care further impact neurodevelopment [11]. These temporal and multifactorial influences underscore the complexity of predicting outcomes in this vulnerable population. Despite growing awareness, the predictive accuracy for neurodevelopmental outcomes remains limited, largely due to challenges in integrating the diverse range of contributing factors into a unified model. Previous studies have often focused on isolated variables, such as gestational age or birth weight, neglecting the cumulative and interactive effects of multiple influences [12]. This reductionist approach hampers comprehensive understanding and limits the development of tailored interventions to optimize neurodevelopmental trajectories.

In recent years, advancements in sophisticated statistical methods and artificial intelligence have enabled the development of more accurate predictive models. These techniques allow for the integration of multidimensional data, facilitating the construction of comprehensive models that account for numerous influencing factors. Such models hold promise for more precise risk stratification and the personalization of care plans based on individual risk profiles. Incorporating these predictive tools into clinical practice could significantly enhance neonatal care and neurodevelopmental monitoring. Although several models have been proposed to predict neurodevelopmental outcomes [13, 14], many are limited by small sample sizes, lack of validation in diverse populations, and failure to include possibly relevant variables. Consequently, there is a continuing need for research to identify key influencing factors and to test and refine predictive models across varied cohorts. Additionally, the integration of genetic, epigenetic, and socio-environmental data remains underexplored and represents a promising avenue for future research. In this study, we aimed to identify the influencing factors and develop a comprehensive predictive model for neurodevelopmental outcome in PLBW infants.

Materials and methods

Study design and grouping criteria

This retrospective study analyzed data from 146 PLBW infants who underwent neurodevelopmental assessments at the Women and Children's Hospital of Ningbo University between August 2022 and August 2024. Neurodevelopment was evaluated using the Bayley Scales of Infant Development at a corrected age of two years, calculated as the chronological age minus the gestational age deficit at birth.

Bayley Scales assess cognitive, language, and motor development. Examinations were conducted in a standardized setting by trained professionals to ensure task appropriateness for each infant's developmental level. Each task was scored according to performance, and domain-specific scores were converted to standardized scores, providing a comprehensive profile of developmental status [15, 16]. Based on the results, infants were categorized into two groups. The Normal Neurodevelopmental Outcome (NNO) group included 85 infants with normal neurodevelopment, defined as a Bayley Mental Index score above 84. The Adverse Neurodevelopmental Outcome (ANO) group consisted of 61 infants with mild to severe abnormalities: mild cases included tone or reflex abnormalities without functional impairment and/or a borderline Bayley Mental Index score of 71-84, while severe cases included conditions such as spastic hemiplegia, diplegia, or tetraplegia in non-ambulant children and/or a Bayley Mental Index score below 71. The Guttman split-half reliability coefficient for the Bayley Scales of Infant Development was greater than 0.8 [17].

An external validation cohort of 71 infants meeting the same inclusion criteria was used to assess the model's stability and reliability. These infants were also classified into the NNO and ANO groups according to their Bayley Mental Index scores.

Inclusion and exclusion criteria

Eligible participants were infants born at less than 37 weeks of gestation and weighing under

2,500 grams, with complete medical records and neurodevelopmental assessments conducted at a corrected age of two years using the Bayley Scales.

Exclusion criteria included mortality during hospitalization, congenital anomalies, congenital brain developmental defects, diagnosed genetic metabolic disorders, or confirmed chromosomal abnormalities.

Ethics statement

This study was approved by the Institutional Review Board and Ethics Committee of the Women and Children's Hospital of Ningbo University. Patient information and data were collected by the hospital's medical record system. As the study exclusively used de-identified data and posed no risk to participants, the requirement for informed consent was waived in accordance with relevant ethical and regulatory guidelines for retrospective research.

Data collection

Data were extracted from the medical record system and included demographic characteristics, maternal health information, delivery details, neonatal cranial ultrasound findings, complications, and treatment interventions. Follow-up evaluations were conducted at discharge and again at a corrected age of two years.

Neonatal cranial ultrasound scans were performed two to four times during the first week of life and subsequently one to two times per week until discharge. Scans were conducted through the anterior fontanelle using a portable color Doppler ultrasound device (Vivid i, GE Healthcare, USA) with a probe frequency of 7.5-10 MHz.

Statistical analysis

Data were analyzed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized as counts and percentages [n (%)]. Chi-square or Fisher's exact tests were applied based on sample size and expected frequencies. Continuous variables were assessed for normality with the Shapiro-Wilk test; normally distributed variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and compared using t-tests with variance correction if needed. A p-value <0.05 was considered significant.

Univariate and multivariate logistic regression analyses were conducted to identify risk factors. Receiver Operating Characteristic (ROC) analysis was performed to evaluate model performance, and a predictive model for neurodevelopmental outcomes was constructed. To improve model calibration, Platt Scaling was applied to the logistic regression outputs by fitting a sigmoid function to the log-odds predictions.

Results

Comparison of basic data

The demographic and clinical characteristics of the NNO and ANO groups were generally comparable (**Table 1**). No significant differences were found in gestational age, birth weight, maternal age, education level, primiparity rate, prenatal steroid use, cesarean delivery rate, incidence of premature rupture of membranes, or neonatal Apgar scores (all P>0.05). The proportions of male infants and pregnancies conceived via IVF also did not differ significantly between groups (all P>0.05).

Comparison of neonatal outcomes and complications

The ANO group demonstrated significantly higher rates of hemorrhagic and ischemic cerebral lesions than the NNO group (both P<0.05), while other lesion types did not differ significantly (P>0.05, **Table 2**). Bronchopulmonary dysplasia (BPD) was also more prevalent in the ANO group (P<0.05). No significant differences were found in the incidence of neonatal respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, hypoglycemia, or sepsis (all P>0.05). The ANO group required longer durations of mechanical ventilation and oxygen therapy compared to the NNO group (both P<0.05). The rate of ibuprofen administration did not differ between groups (P>0.05).

Univariate logistic regression analysis of neurodevelopmental outcomes in PLBW infants

Table 3 summarizes the univariate logistic regression analysis examining associations be-

Table 1. Comparison of demographic characteristics between two groups

Data	NNO group (n=85)	ANO group (n=61)	t/χ^2	P
Gestational age (weeks)	34.71 ± 1.12	34.34 ± 1.35	1.812	0.072
Birthweight (g)	2215.34 ± 117.82	2230.51 ± 115.07	0.775	0.440
Boys [n (%)]	51 (60%)	45 (73.77%)/16 (26.23%)	2.991	0.084
IVF [n (%)]	19 (22.35%)	20 (32.79%)	1.975	0.160
Bayley Mental Index	90.95 ± 2.91	70.28 ± 5.23	27.899	<0.001
Maternal age (years)	31.02 ± 4.28	30.52 ± 4.41	0.687	0.493
Maternal education (years)	11.77 ± 5.34	11.86 ± 2.62	0.142	0.887
Primipara [n (%)]	71 (83.53%)	49 (80.33%)	0.249	0.618
Prenatal Steroid Use [n (%)]	46 (54.12%)	33 (54.1%)	0	0.998
Cesarean Delivery [n (%)]	30 (35.29%)	19 (31.15%)	0.274	0.601
Premature Rupture of Membranes [n (%)]	34 (40%)	24 (39.34%)	0.006	0.936
Apgar score 1 min	7.24 ± 2.11	7.25 ± 2.15	0.037	0.971
Apgar score 5 min	8.72 ± 1.51	8.62 ± 1.48	0.393	0.695

NNO: Normal Neurodevelopmental Outcome; ANO: Adverse Neurodevelopmental Outcome; IVF: in vitro fertilization.

Table 2. Comparison of examination, diagnosis, and treatment between two groups

Data	NNO group (n=85)	ANO group (n=61)	t/χ^2	P
Neonatal cerebral ultrasound findings				
Hemorrhagic lesions [n (%)]	12 (14.12%)	20 (32.79%)	7.233	0.007
Ischemic lesions [n (%)]	15 (17.65%)	25 (40.98%)	9.723	0.002
Other lesions [n (%)]	19 (22.35%)	12 (19.67%)	0.153	0.696
Complications during hospitalization				
NRDS [n (%)]	42 (49.41%)	33 (54.1%)	0.312	0.576
BPD [n (%)]	41 (48.24%)	44 (72.13%)	8.337	0.004
PDA [n (%)]	18 (21.18%)	15 (24.59%)	0.237	0.627
NEC [n (%)]	5 (5.88%)	5 (8.2%)	0.046	0.831
ROP [n (%)]	38 (44.71%)	30 (49.18%)	0.286	0.593
Hypoglycemia [n (%)]	15 (17.65%)	12 (19.67%)	0.097	0.756
Sepsis [n (%)]	24 (28.24%)	18 (29.51%)	0.028	0.867
Treatment measures				
Duration of Mechanical Ventilation (days)	14.51 ± 4.37	17.08 ± 6.53	2.677	0.009
Duration of Oxygen Therapy (days)	45.71 ± 14.89	53.28 ± 17.37	2.826	0.005
Use of Ibuprofen [n (%)]	8 (9.41%)	2 (3.28%)	1.243	0.265

NNO: Normal Neurodevelopmental Outcome; ANO: Adverse Neurodevelopmental Outcome; NRDS: Neonatal Respiratory Distress Syndrome; BPD: Bronchopulmonary Dysplasia; PDA: Patent Ductus Arteriosus; NEC: Necrotizing Enterocolitis; ROP: Retinopathy of Prematurity.

tween clinical variables and neurodevelopmental outcomes in PLBW infants. Hemorrhagic lesions, ischemic lesions, BPD, duration of mechanical ventilation, and duration of oxygen therapy emerged as statistically significant predictors of adverse neurodevelopmental outcomes. Each variable demonstrated a positive association, with higher odds of an adverse outcome corresponding to the presence of these complications or extended respiratory support. Wald test results and confidence intervals for the odds ratios confirmed the significance of these relationships.

Multivariate logistic regression analysis of neurodevelopmental outcomes in PLBW infants

Variables identified as significant by the univariate analysis including hemorrhagic lesions, ischemic lesions, BPD, duration of mechanical ventilation, and duration of oxygen therapy were included in the multivariate logistic regres-

Table 3. Univariate logistic regression analysis of neurodevelopmental outcomes in PLBW infants

Data	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Hemorrhagic lesions [n (%)]	1.088	0.414	2.627	0.008	2.967	1.335	6.843
Ischemic lesions [n (%)]	1.176	0.386	3.049	0.002	3.241	1.539	7.030
BPD [n (%)]	1.022	0.359	2.848	0.004	2.778	1.393	5.712
Duration of Mechanical Ventilation (days)	1.363	0.378	3.608	<0.001	3.908	1.888	8.351
Duration of Oxygen Therapy (days)	1.080	0.362	2.983	0.002	2.945	1.460	6.064

PLBW: Preterm Low Birth Weight; BPD: Bronchopulmonary Dysplasia.

Table 4. Multivariate logistic regression analysis of neurodevelopmental outcomes in PLBW infants

Data	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Hemorrhagic lesions [n (%)]	1.107	0.463	2.392	0.016	3.024	1.221	7.490
Ischemic lesions [n (%)]	1.088	0.424	2.565	0.010	2.968	1.293	6.816
BPD [n (%)]	0.841	0.396	2.124	0.033	2.319	1.067	5.039
Duration of Mechanical Ventilation (days)	0.076	0.036	2.111	0.034	1.079	1.005	1.157
Duration of Oxygen Therapy (days)	0.032	0.012	2.572	0.010	1.032	1.008	1.058

PLBW: Preterm Low Birth Weight; BPD: Bronchopulmonary Dysplasia.

Table 5. ROC analysis of neurodevelopmental outcomes in PLBW infants

Data	Best threshold	Sensitivities	Specificities	AUC	Youden index	F1 score
Hemorrhagic lesions [n (%)]	0.500	0.328	0.859	0.593	0.187	0.430
Ischemic lesions [n (%)]	0.500	0.410	0.824	0.617	0.234	0.495
BPD [n (%)]	0.500	0.721	0.518	0.619	0.239	0.603
Duration of Mechanical Ventilation (days)	18.100	0.475	0.812	0.634	0.287	0.547
Duration of Oxygen Therapy (days)	55.265	0.475	0.765	0.637	0.240	0.527

PLBW: Preterm Low Birth Weight; BPD: Bronchopulmonary Dysplasia.

sion (**Table 4**). All retained statistical significance, confirming their independent associations with adverse neurodevelopmental outcomes. Odds ratios for all variables exceeded 1, indicating an increased likelihood of unfavorable outcomes in the presence of these factors or longer respiratory support durations.

ROC analysis

ROC analysis was performed to evaluate the predictive accuracy of individual parameters for adverse neurodevelopmental outcomes in PLBW infants (**Table 5**). Hemorrhagic and ischemic lesions exhibited high specificity but relatively low sensitivity, whereas BPD showed high sensitivity with lower specificity. Duration of mechanical ventilation and oxygen therapy yielded the highest AUC values, demonstrating balanced sensitivity and specificity profiles and indicating superior discriminative ability compared to individual complications alone.

Composite predictive model

A composite predictive model incorporating hemorrhagic lesions, ischemic lesions, BPD, duration of mechanical ventilation, and duration of oxygen therapy was constructed to predict neurodevelopmental outcomes in PLBW infants. The model formula is: Y=1.107 × Hemorrhagic lesions [n (%)] + 1.088 × Ischemic lesions [n (%)] + 0.841 × BPD [n (%)] + 0.076 × Duration of Mechanical Ventilation (days) + 0.032 × Duration of Oxygen Therapy (days).

This model demonstrated high predictive value with an AUC of 0.833 (**Figure 1A**). Optimal cut-off values derived from ROC analysis for the included predictors were: hemorrhagic lesions

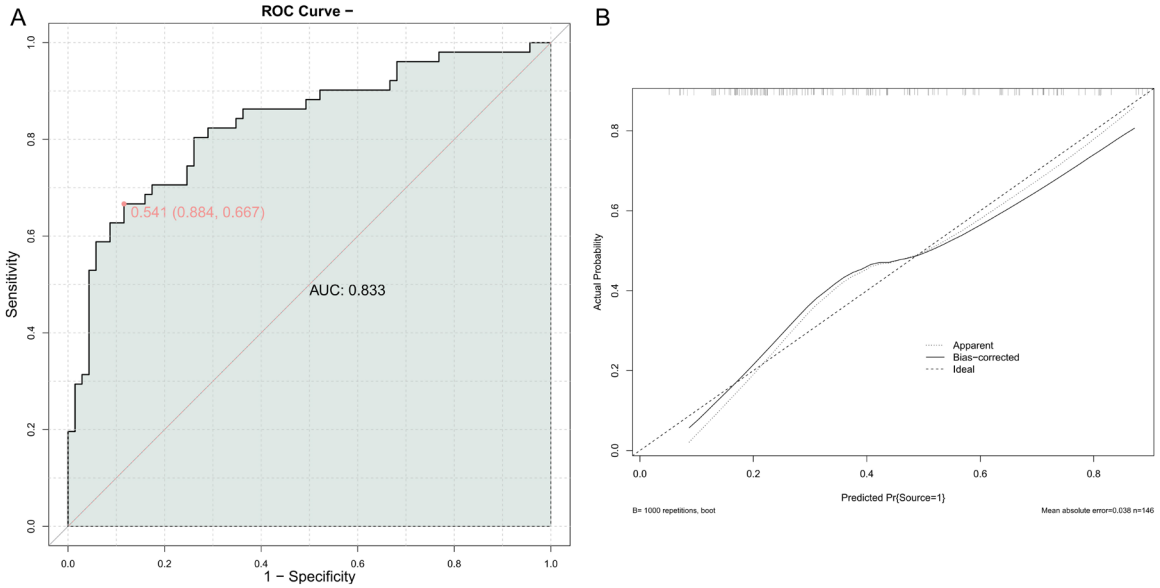

Figure 1. Composite predictive model for neurodevelopmental outcomes in PLBW infants. A: ROC Curve; B: Calibration Curve; PLBW: Preterm Low Birth Weight.

(n [%]: 0.5), ischemic lesions (n [%]: 0.5), BPD (n [%]: 0.5), duration of mechanical ventilation (days): 19.2, and duration of oxygen therapy (days): 54.39. These cut-offs maximized the trade-off between sensitivity and specificity. Probability calibration of the logistic regression model was performed using the Platt Scaling method; the resulting calibration curve is shown in **Figure 1B**.

External validation of the predictive model

In the external validation cohort, baseline characteristics - including gestational age, birth weight, sex distribution, maternal age, and prenatal steroid administration - did not differ significantly between infants with NNO and those with ANO (all P>0.05; **Table 6**). Rates of cesarean delivery, premature rupture of membranes, and Apgar scores were also comparable between groups (all P>0.05). However, the ANO group had a significantly higher prevalence of neonatal complications, specifically hemorrhagic and ischemic brain lesions, as well as BPD. Additionally, infants in the ANO group required significantly longer durations of mechanical ventilation and oxygen therapy, consistent with findings from the original test cohort.

ROC analysis in the external validation set

The external validation cohort was used to assess the model's predictive performance beyond the original training dataset. ROC analysis demonstrated that the model maintained robust discriminative ability in this independent sample. Hemorrhagic and ischemic lesions and the duration of mechanical ventilation showed moderate sensitivity but high specificity, while BPD and the duration of oxygen therapy exhibited high sensitivity with lower specificity. Among these factors, the duration of oxygen therapy achieved the highest AUC value (0.702; **Table 7**), followed by ischemic lesions and duration of mechanical ventilation (AUC 0.672-0.702). These results are consistent with those observed in the training cohort, highlighting the predictive importance of prolonged respiratory support and neonatal complications. They underscore the combined use of lesion markers and extended respiratory interventions for predicting neurodevelopmental outcomes.

External validation ROC analysis

ROC analysis in the external validation cohort further confirmed the model's predictive strength (**Figure 2A**). The model achieved an AUC of 0.854, indicating a high capacity to distinguish between favorable and unfavorable neurodevelopmental outcomes in an independent dataset. The point marked on the ROC curve, with coordinates (0.927, 0.700) and a confidence interval of 0.585, supports the model's robust discrimination capability. Overall, the external validation ROC curve demonstrates the

Table 6. Comparison of demographic characteristics between two groups in the external validation set

Data	NNO group (n=41)	ANO group (n=30)	t/χ^2	P
Gestational age (weeks)	34.69 ± 1.19	34.22 ± 1.34	1.244	0.220
Birthweight (g)	2221.96 ± 117.63	2233.76 ± 115.26	0.338	0.737
Boys [n (%)]	14 (56%)	13 (65%)	0.375	0.540
IVF [n (%)]	5 (20%)	5 (25%)	0.002	0.968
Bayley Mental Index	92.04 ± 2.64	71.39 ± 5.39	15.684	<0.001
Maternal age (years)	31.04 ± 4.41	30.54 ± 4.96	0.355	0.724
Maternal education (years)	11.63 ± 2.67	11.85 ± 2.37	0.285	0.777
Primipara [n (%)]	19 (76%)	18 (90%)	0.686	0.408
Prenatal Steroid Use [n (%)]	15 (60%)	11 (55%)	0.114	0.736
Cesarean Delivery [n (%)]	9 (36%)	6 (30%)	0.180	0.671
Premature Rupture of Membranes [n (%)]	10 (40%)	7 (35%)	0.118	0.731
Apgar score 1 min	7.31 ± 2.11	7.27 ± 2.11	0.053	0.958
Apgar score 5 min	8.61 ± 1.39	8.56 ± 1.53	0.113	0.911
Hemorrhagic lesions [n (%)]	2 (8%)/23 (92%)	8 (40%)/12 (60%)	4.862	0.027
Ischemic lesions [n (%)]	4 (16%)/21 (84%)	9 (45%)/11 (55%)	4.549	0.033
BPD [n (%)]	12 (48%)/13 (52%)	16 (80%)/4 (20%)	4.840	0.028
Duration of Mechanical Ventilation (days)	13.65 ± 4.38	17.35 ± 6.22	2.339	0.024
Duration of Oxygen Therapy (days)	46.07 ± 14.03	57.61 ± 16.15	2.562	0.014

NNO: Normal Neurodevelopmental Outcome; ANO: Adverse Neurodevelopmental Outcome; IVF: In vitro fertilization; BPD: Bronchopulmonary Dysplasia.

Table 7. ROC analysis of neurodevelopmental outcomes in PLBW infants in the external validation set

Data	Best threshold	Sensitivities	Specificities	AUC	Youden index	F1 score
Hemorrhagic lesions [n (%)]	0.500	0.433	0.902	0.668	0.335	0.553
Ischemic lesions [n (%)]	0.500	0.467	0.878	0.672	0.345	0.571
BPD [n (%)]	0.500	0.800	0.537	0.668	0.337	0.658
Duration of Mechanical Ventilation (days)	19.050	0.433	0.902	0.672	0.335	0.553
Duration of Oxygen Therapy (days)	46.500	0.800	0.585	0.702	0.385	0.676

BPD: Bronchopulmonary Dysplasia.

reliability of the developed model in predicting neurodevelopmental outcomes in PLBW infants. The calibration curve (**Figure 2B**) revealed good agreement between predicted probabilities and observed outcomes, indicating satisfactory model calibration and predictive reliability.

Discussion

In this study, we investigated the neurodevelopmental outcomes of PLBW infants and identified key factors influencing these outcomes. Hemorrhagic and ischemic cerebral lesions, BPD, and prolonged durations of mechanical ventilation and oxygen therapy emerged as significant predictors of ANO. These findings are consistent with previous research [18-20], underscoring the detrimental impact of neurological and respiratory complications on developmental trajectories of premature infants.

The prominence of cerebral lesions as predictors highlights the critical role of early neurological insults in shaping long-term neurodevelopment. Hemorrhagic lesions, commonly resulting from intraventricular hemorrhage (IVH), disrupt neuronal connectivity and can cause permanent damage to brain regions essential for cognitive and motor function [21, 22]. IVH, particularly grades III-IV, affects the germinal matrix - a key neurogenic region producing oligodendrocytes and neurons during late gestation. The fragility of immature vasculature, com-

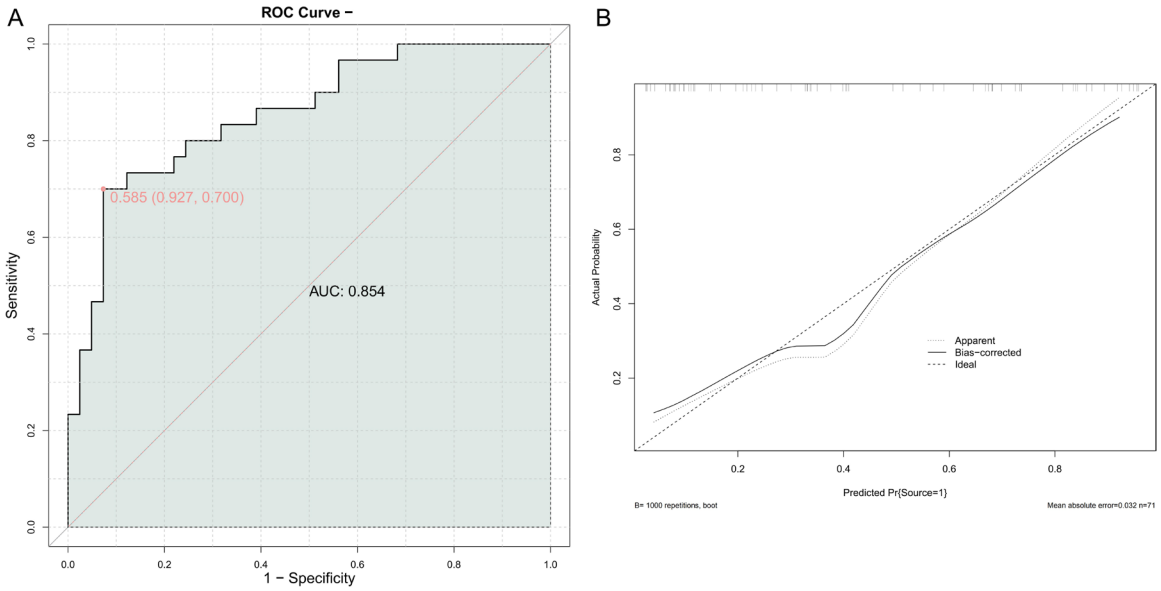

Figure 2. External validation ROC curve and calibration curve. A: ROC Curve; B: Calibration Curve.

bined with fluctuating cerebral blood flow, predisposes preterm infants to hemorrhage, resulting in neuronal loss and gliosis [23, 24]. Ischemic lesions compound these effects by exacerbating cerebral hypoxia, further impairing neuronal maturation and synaptogenesis [25]. Ischemic injuries, such as periventricular leukomalacia (PVL), reflect hypoxic-ischemic damage to developing white matter tracts. Oligodendrocyte progenitor cells are especially vulnerable to glutamate excitotoxicity and free radical damage during hypoxic episodes, disrupting myelination and axonal connectivity [26, 27]. Cerebral lesions trigger secondary cascades, including neuroinflammation, oxidative stress, and altered neurotransmitter dynamics. For example, microglial activation releases pro-inflammatory cytokines (e.g., TNF-α, IL-6), impairing synaptic pruning and neurogenesis, while iron deposition from hemorrhage amplifies oxidative damage, further compromising neuronal survival [23]. Together, these mechanisms likely contribute to the long-term neurodevelopmental deficits observed in the ANO group.

The association between BPD and adverse outcomes highlights the intricate interplay between respiratory and neurological development. BPD, marked by impaired alveolar growth and prolonged oxygen dependence, may affect neurodevelopment through systemic and cerebral hypoxia, oxidative stress, and chronic inflammation [28-30]. Alveolar dysfunction in BPD perpetuates intermittent hypoxemia, precipitating hypoxic-ischemic episodes in the developing brain. Sustained hypoxia downregulates vascular endothelial growth factor (VEGF), impeding angiogenesis and exacerbating white matter injury. Additionally, hypoxia-inducible factors (HIFs) modify gene expression, promoting inflammation and neuronal apoptosis [31]. These pathophysiologic processes disrupt myelination and cortical development, ultimately impairing cognitive and motor functions. Moreover, prolonged mechanical ventilation and oxygen therapy increase the risk of infection, ventilator-associated lung injury, and cerebral perfusion fluctuations, further jeopardizing neurological integrity. Our findings emphasize the significance of extended respiratory support as a critical determinant of neurodevelopment. Prolonged ventilation and oxygen therapy reflect severe respiratory compromise and physiological vulnerability. The association between respiratory interventions and neurodevelopmental impairment may involve sustained hypoxia, mechanical instability of cerebral blood flow, and secondary neuroinflammation [32-34]. These factors collectively alter brain structure and neurochemical balance, impeding the maturation of essential neural networks [35, 36].

Furthermore, the study's multivariate analysis underscores the independent contribution of

each factor to neurodevelopmental outcomes. This indicates that although individual predictors are significant, their combined effects - reflecting the cumulative burden of neonatal morbidity - should be prioritized in both clinical practice and research. The composite predictive model illustrates the additive risk posed by co-occurring factors, highlighting the need for integrated interventions that address multiple organ systems simultaneously. Supported by robust ROC analysis, the predictive model shows strong potential for clinical use as an early warning tool to identify infants at elevated risk.

These findings have important clinical implications. Early identification of high-risk infants using predictive models mat help optimize neonatal care and resource allocation. Targeted monitoring and timely interventions may mitigate neurodevelopmental impairments in vulnerable infants. Furthermore, insights into underlying mechanisms - such as hypoxia and inflammation - could inform the development of novel neuroprotective strategies. The model also supports multidisciplinary care by enabling neonatologists to communicate long-term risks to families and by guiding rehabilitation teams in designing personalized care plans.

To maximize its clinical impact, future work should focus on the following:

Integration with Electronic Health Records (EHRs): Embedding automated risk score calculations into EHR systems to provide real-time alerts and clinical decision support.

Cost-Effectiveness Analysis: Evaluating the economic benefits of model-informed early interventions, such as reduced readmission rates and improvements in quality-adjusted life years.

Expansion to Predict Secondary Outcomes: Adapting the model to forecast additional neurodevelopmental conditions, including autism spectrum disorder and school-age cognitive impairments.

Addressing these aspects could transform neonatal care from a reactive, survival-focused approach to a proactive, precision-based strategy aimed at optimizing long-term neurodevelopmental trajectories.

Nevertheless, this study had limitations. Its retrospective single-center design may have limited the generalizability of the findings. The overall sample size, including the external validation cohort, was relatively small, possibly affecting statistical power and the robustness of model validation. Additionally, the study did not assess antenatal or postnatal environmental influences, such as socioeconomic status, parental education, or caregiver support, which could have impacted neurodevelopmental outcomes. Future research should include larger, multicenter, prospective cohorts with longitudinal follow-up to validate these findings and explore additional risk factors.

In conclusion, this study identifies key factors associated with neurodevelopmental outcomes in PLBW infants, emphasizing the significant roles of cerebral lesions and respiratory complications. The developed predictive model offers a valuable tool for early risk identification and targeted intervention, with the potential to improve long-term outcomes. Continued research to elucidate and address the complex pathways linking prematurity, respiratory support, and neurodevelopment is essential for advancing care in this high-risk population. Ongoing efforts to develop innovative therapies and refine risk stratification methods remain critical to reducing the global burden of neurodevelopmental impairment.

Disclosure of conflict of interest

None.

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