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Original Research

An Exploratory Study of a Prognostic Risk Warning Model for Neonatal Respiratory Distress Syndrome Based on Dynamic Monitoring of Blood Gas: A Prospective Cohort Study

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Abstract

Background: This study is a prospective cohort study. It aims to investigate the relationship between blood gas parameters and neonatal respiratory outcomes and to develop a prognostic prediction model. **Methods**: A total of 163 preterm newborns who satisfied the diagnostic criteria outlined in the European Guidelines for the Prevention and Treatment of NRDS-2010 from January 2022 to January 2025 were included. The baseline data of mothers and newborns were collected, and the blood gas parameters were dynamically monitored at 6, 12, 24, and 48 h after birth, including pH, oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$), lactic acid (Lac), and oxygenation index (OI), as well as PaO_2/fraction of inspired oxygen (FiO_2). Elastic net regression and the Boruta algorithm were used to screen predictive variables, and a multivariate Cox proportional hazards regression model was established. The performance of the model was evaluated using a time-dependent receiver operating characteristic (ROC) curve, Bootstrap resampling calibration curve, and decision curve analysis (DCA). **Results**: The poor prognosis group (n = 30) experienced a higher rate of maternal pregnancy comorbidities (50.0% vs. 26.3%; $p = 0.011$), had a smaller gestational age (29.4 weeks; $p = 0.019$), lower birth weight (1412.5 g; $p < 0.001$) and 5-minute Apgar score ($p = 0.034$), and a higher need for initial mechanical ventilation (53.3% vs. 27.1%; $p = 0.005$). Dynamic monitoring revealed significant acidosis in the early phase (6 hours), which remained at persistently low levels even at 48 hours. The OI progressively increased, oxygenation efficiency declined, and lactate clearance was markedly delayed. Elastic net regression (optimized $\lambda = 0.1759$ via 10-fold cross-validation) and Boruta algorithm screening identified core variables for inclusion in a multivariate Cox regression. Meanwhile, △OI_24 h (hazard ratio (HR) = 1.82, 95% confidence interval (CI) 1.51–2.21; $p < 0.001$) and Lac_48 h (HR = 1.95, 95% CI: 1.40–2.73; $p < 0.001$) were identified as independent risk factors. The model predicted a 7-day poor prognosis with an area under the ROC curve of 0.96 (95% CI 0.92–1.00). A 1000 Bootstrap validation model demonstrated high concordance between predicted and actual risks. The DCA indicated that the model provided a significant clinical net benefit compared to intervention or no intervention strategies when the risk threshold exceeded 0.15. **Conclusions**: △OI_24 h and Lac_48 h serve as core early warning indicators for poor prognosis in NRDS. The model was constructed using elastic net regression and the Boruta algorithm, demonstrating robust predictive performance and clinical utility, and providing a basis for early risk stratification.

Keywords: neonatal respiratory distress syndrome; dynamic monitoring of blood gas; oxygenation index; prognosis; elastic net regression; Boruta algorithm; Cox proportional risk model

1. Introduction

Neonatal respiratory distress syndrome (NRDS), is a primary reason for morbidity and mortality among premature newborns, involving progressive alveolar degeneration and ventilation/blood flow disproportion due to deficient lung active substance [1]. Advancements in perinatal medicine technology, along with prenatal hormone prophylaxis and postnatal lung surfactant therapy, have notably increased the survival chances of newborns with NRDS, although the clinical prognosis remains highly heterogeneous [2,3]. Some newborns rapidly encounter severe complications, including persistent hypoxemia and pneumothorax, and may die despite active efforts to intervene [4]. The morbidity and mortality rate for newborns suffering from severe NRDS can surpass 20%, as per statistics, and survivors are more likely to develop sequelae like bronchopulmonary dysplasia [5].

The prognostic assessment system for NRDS is facing a paradigm shift from static anatomic evaluation to dynamic functional monitoring. In modern medical practice, despite the continued use of traditional markers such as gestational age, birth weight, Apgar score, and chest radiograph grading for initial risk classification, their ability to predict outcomes declines significantly during disease progression [6,7]. This limitation stems from the underlying spatiotemporal heterogeneity of the pathophysiological processes in NRDS [8,9]. Decreased lung compliance triggered by alveolar surface-active substance deficiency is only one part of the disease phenotype, and the resulting cascade of responses, including ventilation/blood flow dysregulation due to pulmonary vasoconstriction, pulmonary

edema triggered by altered alveolar-capillary barrier permeability, deterioration of oxygenation due to increased right-to-left shunting, and secondary respiratory muscle fatigue and increased respiratory work, constitute a multidimensional dynamic regulatory network.

Blood gas analysis is being reconsidered for its clinical significance in reflecting respiratory-metabolic coupling [10]. Traditional monitoring focuses on the instantaneous values of isolated parameters such as partial pressure of O_2 (PaO_2), partial pressure of CO_2 ($PaCO_2$), and pH, but ignores the temporal evolutionary characteristics of these indicators. For example, simply maintaining PaO_2 in the normal range may mask the progression of lung injury due to alveolar hyperexpansion under the support of mechanical ventilation, whereas compensatory stabilization of pH may delay the detection of respiratory failure thresholds [11]. Recent studies have revealed that the dynamic coupling relationship between lactate clearance (Lac clearance) and oxygenation index (OI) can more precisely indicate the alignment of tissue perfusion and oxygen use [12,13]. The pathophysiologic process of NRDS is dynamic and continuous, involving multidimensional interactions of impaired oxygenation, ventilation failure, acidosis and compensatory metabolic changes. Especially for newborns who have been on respiratory support, identifying high-risk newborns who seem stable but are on the verge of collapse through ongoing, multidimensional blood gas parameter monitoring is a significant hurdle. However, existing studies have focused on OI or traditional blood gas indices at a single time point, and there is a lack of systematic exploration of the synergistic patterns of changes in blood gas indices (including basal parameters, such as pH, PaO_2, and derived parameters, such as OI and PaO_2/fraction of inspired oxygen (FiO_2)) at multiple time points and in multiple dimensions in the critical postnatal window (e.g., within the first 48 h after birth) of newborns with NRDS. There is no systematic exploration of constructing a prognostic warning model based on such dynamic changes. Prognostic and early warning modeling.

Therefore, there is an urgent clinical need to fill the research gap on the association between dynamic monitoring of blood gas and NRDS prognosis and to establish an early risk stratification tool. This research gathered dynamic blood gas data in multiple dimensions at 6, 12, 24, and 48 h after birth from newborns with NRDS, along with the birth characteristics of the mothers and the newborns. The aim is to reveal the characteristic blood gas evolution patterns of newborns with poor prognosis, identify key early warning indicators such as OI and metabolic compensation patterns, and construct a Cox proportional risk early warning model integrating dynamic blood gas parameters and clinical variables, which will ultimately provide a quantitative tool to realize early risk identification and precise intervention to improve the prognosis of newborns with NRDS.

2. Materials and Methods

2.1 Subjects

This study was a prospective cohort study. Patients were newborns enrolled in diagnosed cases of NRDS meeting criteria from January 2022 to January 2025 at The First Affiliated Hospital of Anhui Medical University. Inclusion criteria: (1) compliance with the European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update [14], regarding clinical symptoms and imaging data; (2) single fetus; (3) gestational age $\leq$37 weeks and birth weight $<$2500 g. Exclusion criteria: (1) congenital developmental anomalies, inherited metabolic and chromosomal disorders; (2) severe intrauterine infections (e.g., sepsis); and (3) severe asphyxia (Apgar score $\leq$3 and lasting for 10 minutes), as well as abandonment of treatment, or missing data $>$20%. The data were then obtained from the records related to newborns who met the above inclusion and exclusion criteria, and 163 subjects were finally included. The study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (Ethical approval number: No. 2021AMU-0532), and the guardians of the newborns voluntarily signed an informed consent form.

2.2 Information Collection

Maternal information: age, gestational comorbidities (e.g., gestational diabetes mellitus or hypertension), prenatal hormone use, and mode of delivery (eutocia or cesarean section) were recorded.

Neonatal information: gestational age, birth weight, gender, Apgar scores at 1 and 5 minutes (1-min Apgar and 5-min Apgar), initial respiratory support (non-invasive continuous positive airway pressure [CPAP] or mechanical ventilation, initial respiratory support equipment including Weikang V60 (Shenzhen Weikang Biological Technology Co., Ltd., Shenzhen, Guangdong, China) non-invasive ventilator 25A (Delgado Medical Systems, Frankfurt, Germany) for non-invasive CPAP treatment, Delgado Evita XL invasive ventilator for mechanical ventilation treatment), and chest X-ray classification (grade I–IV based on the severity of NRDS). Chest X-ray examination was performed using Philips DigitalDiagnost DR chest X-ray machine (C90, Philips Healthcare, Amsterdam, The Netherlands) [14].

2.3 Neonatal Blood Gas Procedure

Radial artery or dorsalis pedis artery (preferred arterial catheter) was selected and sterilized with 75% alcohol twice. Blood samples (0.3–0.5 mL) were collected by puncture using a heparinized syringe, gently mixed for anticoagulation, and sent for testing within 15 min. Testing was performed using the Siemens Rapidpoint 500 blood gas analyzer (Siemens Healthineers, Erlangen, Germany). Blood collection time, site and newborn status were recorded to avoid hemolysis or air bubble interference. The device was

calibrated daily, with abnormal results (e.g., pH <7.0) requiring retesting for confirmation.

2.4 Dynamic Monitoring of Blood Gas

Blood gas levels were dynamically monitored at several time points: within 6 h of birth (baseline), and at 12, 24, and 48 h after birth, as well as during any condition worsening, like a sudden decrease in the oxygenation index or the need to adjust the ventilator parameters. In terms of monitoring indicators, pH, PaO_2, $PaCO_2$, HCO_3^-, base excess (BE), and Lac were monitored. The derived indicators, i.e., OI (FiO_2 $\times$ mean airway pressure $\times$ 100/PaO_2) and PaO_2/FiO_2 ratio were also measured.

2.5 Endpoints

The endpoint metrics consisted of primary and secondary outcomes. The primary outcomes were a poor prognostic composite endpoint that encompassed death in the first week after birth, pneumothorax or mediastinal emphysema requiring closed chest drainage, and severe respiratory failure requiring high-frequency oscillatory ventilation support for >24 h high-frequency oscillatory ventilation equipment utilized was the Stephanie BabyLog 8000+ ventilator (Stephan Medizintechnik GmbH, Gackenbach, Germany). The secondary endpoints included changes in dynamic blood gases within 24 h and within 24–48 h of birth.

2.6 Sample Size Estimation

The required sample size (N) must satisfy the following criteria: limiting overfitting: $N \geq k/(R^2 \times 0.05)$; accurate variable estimation of the number of events: $E \geq 10 \times k$. Here, k represents the expected number of predictor variables included in the model, R^2 denotes the expected model explanatory power (set at 0.20), and E is the required number of events.

Based on preliminary studies and literature, k = 4 was set. Substituting into the formula yields a required event count of 40. This study ultimately enrolled 163 pediatric patients, with 30 events. While the total sample size did not fully meet the theoretical calculation, it reached a common scale for this type of research.

2.7 Statistical Analysis

Statistical analyses were performed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA). To evaluate the normality of the data, Shapiro-Wilk tests were conducted. Continuous variables conforming to normal distribution were expressed as mean $\pm$ standard deviation (SD), and differences between groups were compared by independent samples *t*-test. Non-normally distributed data were described by median [M (Q1, Q3)], and Mann-Whitney U-test was applied for comparison between groups; and categorical variables were expressed as frequency (percentage) [n (%)] and analyzed for between-group differences by chi-square test. The magnitude of change in key blood gas indices (e.g., pH, PaO_2, $PaCO_2$, etc.) was assessed by calculating the difference between the 24-hour value and the 6-hour baseline value and the difference between the 48-hour value and the 24-hour value. Using two robust feature selection methods—Elastic Net regression and the Boruta algorithm—predictors were screened from all clinical baseline characteristics and dynamic blood gas parameters. Ultimately, four core dynamic blood gas parameters were selected for inclusion in the final model. Subsequently, a multivariable Cox proportional hazards regression model was established. The time-dependent receiver operating characteristic (ROC) curve (7 days) of the predictive model was plotted for evaluation. To assess model calibration, 1000-sample Bootstrap internal validation was performed, and a calibrated calibration curve was plotted. Finally, decision curve analysis (DCA) was conducted to evaluate the clinical net benefit of the model at different risk thresholds. All statistical tests were completed using specialized software with two-sided test level $\alpha = 0.05$, and $p < 0.05$ was considered statistically different.

3. Results

3.1 Clinical Characteristics of Newborns With NRDS

This study included 163 newborns with NRDS who were categorized into a good prognosis group (n = 133) and a poor prognosis group (n = 30) based on the composite endpoints. As for maternal baseline characteristics, there were no significant differences between the two groups in terms of age (p = 0.076) and prenatal hormone use (p = 0.659) and cesarean section rate (p = 0.322), but there was a significantly higher incidence of pregnancy comorbidities in the poor prognosis group (50.0% *vs*. 26.3%, p = 0.011). Based on neonatal characteristics, gestational age (p = 0.019), birth weight ($p < 0.001$), and 5-min Apgar (p = 0.034) were significantly lower in the poor prognosis group than in the good prognosis group, whereas the differences in gender (p = 0.583), 1-min Apgar (p = 0.056). Although the proportion of chest radiographs graded $\geq$II was higher in the poor group (40.0% *vs*. 28.6%), it did not reach a significant level (p = 0.220). Notably, there was a significant difference in the mode of initial respiratory support between the two groups: 53.3% of the poor prognosis group directly required mechanical ventilation, whereas only 27.1% of the good group did so. Accordingly 72.9% of the good group initiated treatment with CPAP, which was significantly higher than the 46.7% in the poor group (p = 0.005). These findings suggest that maternal pregnancy comorbidities, low gestational age, low birth weight and initial need for mechanical ventilation may be strongly associated with poor prognosis in newborns with NRDS (Table 1).

3.2 Blood Gas Analysis in Newborns With NRDS

Neonatal blood gas indices in the poor and good prognosis groups were dynamically monitored (Table 2), and significant differences were found between the two groups

Table 1. Comparison of baseline characteristics.

Variables	Total (n = 163)	Poor prognosis group (n = 30)	Good prognosis group (n = 133)	*p* value
Maternal information				
Age, years	32.7 (29.6, 35.2)	33.5 (32.8, 36.6)	32.10 (29.4, 34.8)	0.076
Gestational comorbidities	50 (30.7)	15 (50.0)	35 (26.3)	0.011
Prenatal hormone use	82 (50.3)	14 (46.7)	68 (51.1)	0.659
Mode of delivery (cesarean section)	90 (55.2)	19 (63.3)	71 (53.4)	0.322
Neonatal information				
Gestational age, weeks	30.2 (28.7, 31.8)	29.4 (28.0, 30.5)	30.6 (28.9, 31.9)	0.019
Birth weight, g	1598.0 (1400.0, 1820.0)	1412.5 (1353.8, 1536.5)	1650.0 (1426.0, 1920.0)	<0.001
Gender (male)	85 (52.2)	17 (56.7)	68 (51.1)	0.583
1-min Apgar	6 [4, 7]	5 [4, 7]	6 [4, 7]	0.056
5-min Apgar	8 [6, 9]	6 [6, 8]	8 [6, 9]	0.034
Chest radiograph classification (II and above)	60 (36.8%)	12 (40.0%)	38 (28.6%)	0.220
Initial respiratory support				0.005
CPAP	111 (68.1%)	14 (46.7%)	97 (72.9%)	
Mechanical ventilation	52 (31.9%)	16 (53.3%)	36 (27.1%)	

CPAP, continuous positive airway pressure; categorical data expressed as n (%) were compared using the chi-square test; continuous values expressed as mean ± standard deviation ($\bar{X}$ ± SD) or median (Q1, Q3) were compared between groups using the Student' *t*-test or the Mann-Whitney U-test. $p < 0.05$ was statistically different.

in some parameters (Table 2). The poor prognosis group showed a triad of evolution of blood gas indicators in comparison with the good prognosis group. A significant acidosis was observed in the early stage (6 h) (pH 7.21 ± 0.10 *vs*. 7.28 ± 0.07), and OI_24–48 h continued to climb (24 h 27.35 ± 3.20 *vs*. 24.03 ± 4.20, 48 h 24.10 ± 3.01 *vs*. 19.88 ± 4.33) accompanied by a decrease in oxygenation efficiency (PaO_2/FiO_2 243.00 ± 45.76 *vs*. 265.35 ± 38.16) with a significant delay in Lac clearance (24 h 2.86 ± 1.17 *vs* 2.15 ± 0.93, 48 h median 2.60 *vs* 1.60 mmol/L). Although the trends of persistent low HCO_3^-, insufficient $PaCO_2$ clearance and BE recovery were not statistically significant, the persistent elevation of 48 h OI and impaired Lac metabolism constituted the most critical early warning indicators, suggesting the existence of a vicious pathological cycle of "early acidosis-progressive oxygenation-delayed metabolic clearance" in poorly prognosticated newborns.

Subsequently, the dynamic characteristics of key blood gas indicators in newborns in the poor prognosis group were compared with those in the good prognosis group, and significant differences were found between the two groups in the magnitude of changes in several indicators (Table 3). In terms of acid-base balance, the increase in pH was greater in the poor prognosis group during the first 24 h after birth ($p = 0.016$), whereas the change in pH tended to slow down during the period of 24–48 h ($p < 0.001$); HCO_3^- showed a more pronounced and sustained increase in the poor prognosis group, which was significantly better than the poor prognosis group at 24 h ($p < 0.001$) and 24–48 h ($p = 0.013$); $PaCO_2$ changes, on the other hand, showed a more significant decrease in the poor prognosis group at 24 h ($p = 0.004$), but not as much improvement as in the good prognosis group at 24–48 h ($p < 0.001$), whereas changes in BE were not statistically different between the two groups. Regarding oxygenation and metabolic indices, OI worsened more significantly in the poor prognosis group at 24 h ($p < 0.001$) and improved less at 24–48 h ($p < 0.001$). Oxygenation efficiency (PaO_2/FiO_2) was more significantly elevated at 24–48 h in the good prognosis group ($p < 0.001$). In terms of Lac clearance, the clearance efficiency was significantly lower in the poor prognosis group than in the good prognosis group both at 24 h ($p < 0.001$) and 24–48 h ($p < 0.001$). Changes in PaO_2 showed a more pronounced rise in the good prognosis group only at 24 h ($p < 0.001$), with no significant difference for the rest of the period.

3.3 Variable Selection Based on Elastic Net and Boruta Algorithms

Elastic Net analysis (**Supplementary Table 1**) identified five non-zero coefficient variables from all candidate variables under the optimal regularization parameter (λ = 0.175894834354564, determined via 10-fold cross-validation; **Supplementary Fig. 1**). The Boruta algorithm (**Supplementary Table 2**, **Supplementary Fig. 2**) further validated the importance of these features. This algorithm explicitly confirmed four variables: △OI_24 h, △$PaCO_2$_24–48 h, △PaO_2_24 h, and Lac_48 h. Among these, △OI_24 h demonstrated significantly higher importance (Mean Importance = 33.1547790) than other variables, establishing its core predictive role. Conversely, △HCO_3^-_24 h was rejected by the algorithm, suggesting its information may be covered by other variables. Both methods jointly identified four core dynamic blood gas

Table 2. Comparison of dynamic blood gas indexes of neonates in two groups.

Variables	Poor prognosis group (n = 30)	Good prognosis group (n = 133)	*p* value
pH value			
Baseline (6 h)	7.21 ± 0.10	7.28 ± 0.07	0.004
12 h	7.28 ± 0.08	7.30 ± 0.07	0.102
24 h	7.36 (7.28, 7.40)	7.36 (7.31, 7.40)	0.382
48 h	7.34 ± 0.09	7.38 ± 0.08	0.031
PaO_2, mmHg			
Baseline (6 h)	54 ± 9	54 ± 9	0.921
12 h	57 ± 9	57 ± 9	0.685
24 h	58 ± 9	60 ± 9	0.306
48 h	61 ± 9	63 ± 9	0.299
$PaCO_2$, mmHg			
Baseline (6 h)	49 ± 9	47 ± 6	0.162
12 h	45 ± 8	43 ± 6	0.374
24 h	42 ± 8	41 ± 6	0.466
48 h	41.26 ± 8.02	38.43 ± 5.90	0.076
HCO_3^-, mmol/L			
Baseline (6 h)	19.45 ± 3.04	20.05 ± 2.85	0.331
12 h	20.74 ± 3.03	21.57 ± 2.88	0.183
24 h	21.89 ± 3.01	23.06 ± 2.84	0.060
48 h	23.45 ± 3.07	25.01 ± 2.90	0.015
BE, mmol/L			
Baseline (6 h)	–4.75 (–5.60, –3.50)	–3.90 (–4.60, –3.50)	0.214
12 h	–2.85 (–3.68, –2.05)	–3.06 ± 1.47	1.000
24 h	–1.65 (–2.17, –0.90)	–1.10 (–2.40, –0.20)	0.297
48 h	–0.10 (–0.80, 0.95)	0.60 (–0.60, 1.50)	0.157
Lac, mmol/L			
Baseline (6 h)	4.16 ± 1.26	3.93 ± 1.01	0.347
12 h	3.51 ± 1.24	3.08 ± 1.07	0.085
24 h	2.86 ± 1.17	2.15 ± 0.93	0.004
48 h	2.60 (1.72, 3.67)	1.60 (1.00, 2.20)	<0.001
OI			
Baseline (6 h)	21.05 ± 3.55	21.35 ± 4.15	0.691
12 h	24.10 ± 3.12	23.42 ± 4.22	0.319
24 h	27.35 ± 3.20	24.03 ± 4.20	<0.001
48 h	24.10 ± 3.01	19.88 ± 4.33	<0.001
PaO_2/FiO_2			
Baseline (6 h)	169.50 ± 43.55	180.15 ± 35.25	0.219
12 h	198.05 ± 46.04	208.10 (183.30, 234.60)	0.200
24 h	225.65 ± 46.41	241.05 ± 37.20	0.098
48 h	243.00 ± 45.76	265.35 ± 38.16	0.017

Continuous data were expressed as mean ± standard deviation ($\bar{X}$ ± SD) or median (Q1, Q3) Student's *t*-test or Mann-Whitney U-test was used for between-group comparisons. $p < 0.05$ was statistically different. PaO_2, oxygen partial pressure; $PaCO_2$, carbon dioxide partial pressure; BE, base excess; Lac, lactate; OI, oxygenation index; FiO_2, fraction of inspired oxygen.

parameters—△OI_24 h, △$PaCO_2$_24–48 h, △PaO_2_24 h, and Lac_48 h—for constructing the final model.

3.4 Multifactor Cox Proportional Hazards Regression Model and Model Performance and Validation

Incorporating the above four variables into a multivariate Cox regression model yielded the results shown in Table 4: △OI_24 h and Lac_48 h were independent risk factors for adverse outcomes within 7 days in children with NRDS. However, △PaO_2_24 h (hazards ratio (HR) = 0.82, 95% confidence interval (CI): 0.66–1.02, p = 0.075) and △$PaCO_2$_24–48 h (HR = 1.22, 95% CI: 0.92–1.62, p = 0.165) did not reach statistical significance (Table 4).

Table 3. Characteristics of changes in blood gas parameters.

Variables	Poor prognosis group (n = 30)	Good prognosis group (n = 133)	*p* value
△PH_24 h	0.11 (0.04, 0.20)	0.08 (0.07, 0.09)	0.016
△PH_24–48 h	0.00 (–0.01, 0.02)	0.02 (0.01, 0.03)	<0.001
△PaO_2_24 h	3.66 ± 1.99	5.35 ± 2.12	<0.001
△PaO_2_24–48 h	2.88 ± 0.73	2.94 ± 0.58	0.673
△$PaCO_2$_24 h	–6.95 ± 2.10	–5.70 ± 1.57	0.004
△$PaCO_2$_24–48 h	–1.30 (–1.50, –0.70)	–2.60 (–3.20, –2.10)	<0.001
△HCO_3^-_24 h	2.45 (2.10, 2.85)	3.00 (2.70, 3.40)	<0.001
△HCO_3^-_24–48 h	1.56 ± 0.78	1.95 ± 0.55	0.013
△BE_24 h	2.96 ± 0.70	2.89 ± 0.69	0.642
△BE_24–48 h	1.62 ± 0.43	1.71 ± 0.45	0.314
△Lac_24 h	–1.31 ± 0.50	–1.78 ± 0.55	<0.001
△Lac_24–48 h	–0.20 (–0.20, –0.10)	–0.50 (–0.60, –0.30)	<0.001
△OI_24 h	6.20 (4.83, 7.33)	2.70 (2.20, 3.20)	<0.001
△OI_24–48 h	–3.25 ± 1.22	–4.15 ± 1.22	<0.001
△PaO_2/FiO_2_24 h	56 ± 12	61 ± 12	0.063
△PaO_2/FiO_2_24–48 h	17 ± 8	24 ± 10	<0.001

Continuous data were expressed as mean ± standard deviation ($\bar{X}$ ± SD) or median (Q1, Q3) using Student's *t*-test or Mann-Whitney U-test for between-group comparisons. $p < 0.05$ was statistically different. ΔPH_24 h is the change in PH at 6 hours versus 24 hours after birth, and ΔPH_24–48 h is the change in pH at 24 hours versus 48 hours after birth.

Table 4. Results of the multivariate Cox proportional hazards model.

Variables	β	S.E	Z	*p* value	HR (95% CI)
△PaO_2_24 h	–0.20	0.11	–1.78	0.075	0.82 (0.66~1.02)
△$PaCO_2$_24–48 h	0.20	0.14	1.39	0.165	1.22 (0.92~1.62)
Lac_48 h	0.67	0.17	3.93	<0.001	1.95 (1.40~2.73)
△OI_24 h	0.60	0.10	6.14	<0.001	1.82 (1.51~2.21)

HR, hazards ratio; CI, confidence interval.

As shown in the time-dependent ROC curve in Fig. 1, the model achieved an area under the curve (AUC) of 0.96 (95% CI: 0.92–1.00) for predicting 7-day adverse outcomes, indicating good discriminatory ability between poor and good outcomes. The adjusted curve obtained through 1000-time internal validation via Bootstrap resampling (Fig. 2A) demonstrates high consistency between predicted and observed risks, indicating excellent predictive accuracy with no significant bias after adjustment. DCA analysis indicated that when the risk threshold exceeded 0.15, the clinical net benefit derived from risk stratification using this predictive model consistently surpassed that of both intervention and no intervention strategies (Fig. 2B). This demonstrates the model's strong clinical utility in supporting decision-making by clinicians.

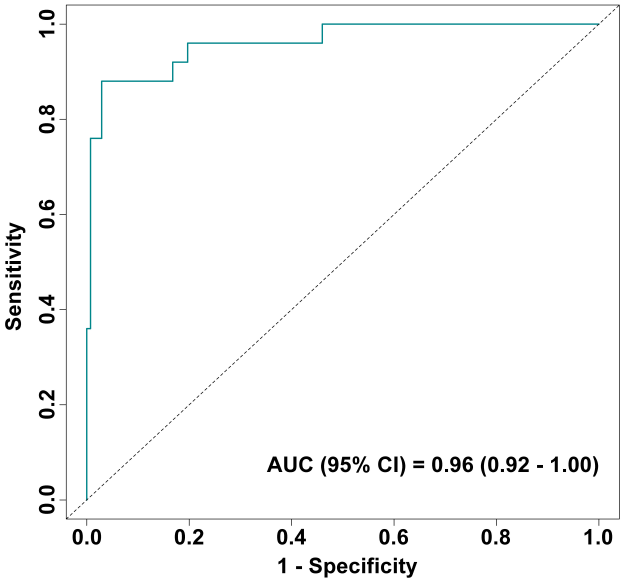

Fig. 1. Time-dependent ROC curve of the predictive model (7 days). AUC, area under the curve.

4. Discussion

This study enrolled 163 preterm infants with NRDS. By integrating dynamic blood gas monitoring data with clinical characteristics, it innovatively employed elastic net regression combined with the Boruta algorithm to optimize variable selection. A prognostic early warning system was

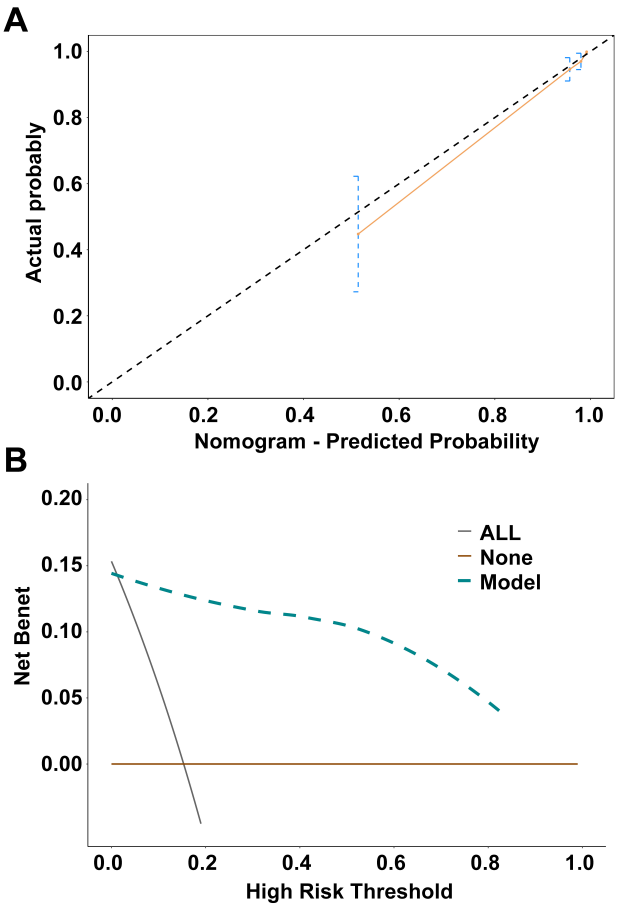

Fig. 2. Internal validation of the model. (A) Calibration curve from internal validation via 1000 Bootstrap resamples. (B) DCA evaluating the model's clinical net benefit at different risk thresholds. DCA, decision curve analysis.

constructed based on a multivariable Cox proportional hazards model. The study not only further validated the association between traditional high-risk factors—such as maternal pregnancy complications and low gestational age—and NRDS prognosis, but also identified the independent predictive value of the 24-hour change in oxygenation index (△OI_24 h) and 48-hour lactate level (Lac_48 h) through refined dynamic indicator analysis and multidimensional model validation, while supplementing the prognostic significance of 5-min Apgar scores and the dynamic range of blood gas indicators. This provides more reliable evidence-based support for the early identification and precise intervention of high-risk NRDS infants.

This study first confirmed the association between maternal pregnancy complications, low gestational age, low birth weight, and initial mechanical ventilation requirements with poor prognosis in preterm infants, consistent with previous research findings [15]. Specifically, the incidence of maternal pregnancy complications was significantly higher in the poor prognosis group than in the good prognosis group, suggesting that pathological conditions during pregnancy (such as gestational diabetes and hypertension) may increase the severity of NRDS by disrupting the fetal lung development microenvironment. Low gestational age and low birth weight reflect the core pathophysiological basis of immature lung tissue development in preterm infants. This finding corroborates previous reports indicating that birth weight <1500 g demonstrates excellent predictive performance for moderate-to-severe bronchopulmonary dysplasia at 14 days postnatal age [16].

Compared with previous studies, this study newly identified an association between the 5-min Apgar score and NRDS prognosis. The 5-min Apgar score was significantly lower in the poor prognosis group than in the good prognosis group, whereas the difference in 1-min Apgar scores was not statistically significant. This finding suggests that the persistence of neonatal resuscitation outcomes (5-min score) better reflects the severity of tissue hypoxia and ischemia than the immediacy (1-minute score). A low 5-min Apgar score typically indicates delayed recovery of respiratory and circulatory function after birth, potentially compounded by NRDS-related ventilatory/oxygenation impairment, thereby exacerbating prognostic risk [17]. Additionally, the initial requirement for mechanical ventilation was significantly higher in the poor prognosis group (53.33%) compared to the good prognosis group (27.07%, $p = 0.005$). This disparity essentially reflects the severity of lung injury: children requiring mechanical ventilation often exhibit more pronounced alveolar collapse and reduced lung compliance, while increased respiratory support intensity indirectly indicates a higher risk of disease progression [18,19]. Notably, the proportion of chest radiographs graded $\geq$II did not reach statistical significance between groups. This may relate to the static anatomical assessment limitations inherent in chest radiography grading. Chest radiographs can only reflect morphological changes of alveolar collapse and cannot capture dynamic functional changes such as ventilation/perfusion matching or metabolic compensation [20]. Therefore, their prognostic predictive value is weaker than that of dynamic blood gas indicators.

Through dynamic monitoring of blood gas parameters at 6, 12, 24, and 48 h, this study identified a triad evolution pattern of "early acidosis-progressive oxygenation impairment-delayed metabolic clearance" in the poor prognosis group. Furthermore, analysis of parameter change magnitudes (e.g., △pH_24 h, △HCO_3^-_24–48 h) revealed the time-dependent characteristics of the pathophysiological process. The poor prognosis group exhibited significant acidosis as early as 6 h postnatal, with a greater pH rebound within 24 h, yet pH improvement stagnated between 24 and 48 h. This phenomenon suggests that the body initially achieves respiratory compensation through hyperventilation, but as lung injury progresses, respiratory compensatory capacity rapidly depletes, forming a temporal boundary between compensation and decompensation [21,22]. Furthermore, the increase in HCO_3^- levels at both

24 h and 24–48 h was significantly lower in the poor prognosis group compared to the good prognosis group. As a core indicator of renal regulation of acid-base balance, the slow rise in HCO_3^- directly reflects the inadequate renal compensatory function in children with poor prognosis. This finding, together with delayed lactate clearance, corroborates the pathological feature of dual respiratory-metabolic dysfunction. Not only is pulmonary ventilation incapable of maintaining acid-base homeostasis, but renal compensatory mechanisms also struggle to offset metabolic acidosis, ultimately leading to persistent deterioration of acid-base imbalance [23,24]. Furthermore, the poor prognosis group exhibited a more pronounced decrease in 24-h $PaCO_2$ but insufficient improvement between 24 and 48 h ($p < 0.001$). This further suggests that while early hyperventilation may temporarily lower $PaCO_2$, it may fail to sustain sustained improvement in ventilation function.

Compared to traditional single-time-point OI (e.g., 48-h OI), △OI_24 h (difference from baseline over 24 h) demonstrated superior prognostic value. The poor prognosis group exhibited higher △OI_24 h values and weaker OI improvement between 24 and 48 h. △OI_24 h directly reflects the "rate of progression" of lung injury, enabling earlier identification of subclinical injury compared to static values [25]. Concurrently, the good prognosis group demonstrated a more significant increase in PaO_2/FiO_2 between 24 and 48 h, validating the positive correlation between dynamic improvement in oxygenation efficiency and prognosis. The poor prognosis group exhibited significantly elevated lactate levels at both 24 and 48 h, accompanied by reduced clearance efficiency. Lac_48 h more accurately reflects metabolic compensation exhaustion than 24-h lactate—delayed clearance at 48 h indicates persistent hypoxia, which can trigger a vicious cycle of myocardial suppression and vascular endothelial dysfunction [26], thereby exacerbating the disease.

This study did not rely on subjective selection variables but instead adopted a data-driven strategy combining elastic net regression (for handling multicollinearity and variable screening) with the Boruta algorithm (a feature importance confirmation algorithm based on random forests) to objectively identify the most predictive variables. The combined approach identified four core dynamic parameters: ΔOI_24 h, $\Delta PaCO_2$_24–48 h, ΔPaO_2_24 h, and Lac_48 h. Among these, ΔOI_24 h (the degree of OI deterioration within 24 h) was assigned significantly higher importance by the Boruta algorithm (Mean Importance = 33.15) compared to other variables, highlighting the central role of early dynamic changes in oxygenation function for prognostic prediction. After incorporating the above variables into a multivariable Cox proportional hazards model, ΔOI_24 h (HR = 1.13, 95% CI: 1.03–1.25, $p = 0.013$) and Lac_48 h (HR = 1.86, 95% CI: 1.15–3.02, $p = 0.012$) were independent risk factors for poor prognosis within 7 days in children with NRDS. A 1-unit increase in ΔOI_24 h elevated the risk of poor prognosis by 82%. Its advantage lies in capturing the early progression trend of lung injury more readily than the static 48-h OI value—even when the 48-h OI does not reach the threshold, an elevated ΔOI_24 h already indicates worsening lung injury, necessitating timely adjustment of respiratory support. Elevated 48-h lactate levels indicated a significantly increased risk, underscoring the importance of ongoing metabolic assessment. While 24-h Lac elevation may reflect transient hypoxia, persistent elevation at 48 h suggests uncorrected metabolic disturbance. This warrants investigation of microcirculatory impairment and infection, along with optimization of perfusion [27].

Limitations

This study has several limitations that warrant caution in interpreting the findings. It is a single-center study with a limited sample size (particularly in the poor prognosis group, n = 30), which may have restricted the power of certain statistical tests and increased the risk of model overfitting. The findings require further validation in prospective, multicenter, large-scale cohort studies. Although the model adjusted for several important variables, unmeasured confounders may still exist. These include detailed ventilator settings strategies, fluid management practices, patent ductus arteriosus and its hemodynamic impact, as well as the specific timing and frequency of surfactant administration—all of which could influence outcomes. The primary outcome of this study was defined as a composite endpoint within 7 days postnatal. These dynamic indicators were not evaluated for their association with longer-term outcomes such as bronchopulmonary dysplasia. Future studies may extend follow-up periods. Based on this, a standardized dynamic monitoring pathway was established using the 6/24/48 h blood gas monitoring points and incorporating △OI_24 h, Lac_48 h into the routine NRDS monitoring indicators. Clinicians can rapidly assess risk using simple calculation formulas without complex equipment, making it suitable for implementation. Additionally, this approach could facilitate the clinical integration of dynamic functional monitoring as an auxiliary criterion for NRDS risk stratification, providing quantitative evidence for developing personalized treatment plans and ultimately improving pediatric patient outcomes. However, it must be emphasized that this study currently offers only preliminary proof-of-concept for this concept. The aforementioned translational application prospects are entirely contingent upon validation of this model in subsequent larger-scale, prospective studies. At the present stage, neither ΔOI_24 h nor Lac_48 h should be used as independent decision-making criteria, and clinical physicians must interpret these metrics holistically in conjunction with the specific circumstances of each pediatric patient.

This study has several limitations that warrant caution in interpreting conclusions and generalizing findings. It is

a single-center observational study with a limited sample size, particularly in the poor prognosis group (n = 30). This limits statistical power, and the generalizability of results requires validation. While the primary composite outcome encompassed severe events, follow-up duration was short (within 7 days). Therefore, the findings cannot infer associations between these dynamic indicators and critical long-term neonatal outcomes (e.g., bronchopulmonary dysplasia, neurodevelopmental prognosis), which are equally vital for assessing the overall burden of NRDS. Although we conducted internal validation using Bootstrap and demonstrated good performance, this remains an internal validation. Whether the model maintains the same predictive efficacy in other populations or medical centers with different clinical practice standards must be confirmed through rigorous external validation. Future studies should involve multicenter collaboration to establish an external validation cohort of $\geq$500 cases. This cohort should validate the predictive accuracy of $\triangle$OI_24 h, Lac_48 h, and model stability, and compare their clinical utility with traditional scoring systems. Follow-up should extend to 40 weeks' corrected gestational age or 1–2 years, incorporating long-term outcomes such as bronchopulmonary dysplasia, Bayley scales, and pulmonary function tests and assessing the predictive value of core indicators for long-term prognosis.

5. Conclusions

The blood gas parameters identified through elastic net regression and the Boruta algorithm—ΔOI_24 h and Lac_48 h—were found to be independent risk factors for poor prognosis in children with NRDS. The predictive model constructed based on these findings demonstrated good discrimination, calibration, and clinical utility in preliminary internal validation, providing proof of concept for a potential early warning tool grounded in objective data. However, before potential clinical implementation, rigorous external validation in larger, heterogeneous cohorts is required, along with optimization incorporating additional clinically relevant variables.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MYZ and YW designed the research study. MYZ performed the research. YW provided help and advice on the experiments. MYZ analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The guardians of the newborns voluntarily signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (approval number: No. 2021AMU-0532).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG44812.

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