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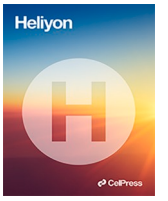

Research article

A nomogram to predict the risk of death during hospitalization in Chinese neonates with respiratory failure

Bo Wang [a,1], Yue Wu [b,1], Jie Shao [c,1], Rui Cheng [b,*], Zuming Yang [d,**], Yan Xu [e,***], Jiangsu Province Neonatal Respiratory Failure Collaborative Group

[a] Department of Neonatology, the Affiliated Suqian First People's Hospital of Nanjing Medical University, Suqian, 223800, China
[b] Department of Neonatology, Children's Hospital of Nanjing Medical University, Nanjing, 210008, China
[c] Department of Neonatology, Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital, Nanjing, 210004, China
[d] Department of Neonatology, Suzhou Municipal Hospital, Suzhou, 215002, China
[e] Department of Neonatology, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221002, China

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ABSTRACT

Background: Neonatal respiratory failure (NRF) is a critical condition with high morbidity and mortality rates. This study aimed to develop a nomogram prediction model to early predict the risk of death in Chinese neonates with NRF.

Methods: A retrospective analysis was conducted on NRF neonates from 21 tertiary neonatal intensive care units (NICUs) across 13 prefecture-level cities in Jiangsu Province, China, from March 2019 to March 2022. NRF neonates from one random NICU were selected as the external validation set, while those from the remaining 20 NICUs were divided into the training set and the internal validation set at a 7:3 ratio. Death was the primary outcome. LASSO regression and multivariate logistic regression were used to identify the predictive factors from the training set and then the nomogram was constructed.

Results: A total of 5387 neonates with NRF were included in the analysis. Among them, 3444 were in the training set, 1470 were in the internal validation set, and 473 were in the external validation set. The nomogram was constructed based on the eight predictors of the 1-min Apgar score, birth weight, gestational age, the relationship between birth weight and gestational age, mode of first respiratory support, inhaled nitric oxide, antenatal corticosteroids, and vasoactive drugs. The area under the curve of the nomogram in the training set, internal validation set, and external validation set was 0.763, 0.733, and 0.891, respectively. The P-values of the Hosmer-Lemeshow goodness of fit test were 0.638, 0.273, and 0.253, respectively. Brier scores were 0.066, 0.072, and 0.037, respectively. The decision curve analysis demonstrated a significant net benefit in all cases. These data indicate the good performance of the nomogram.

Conclusions: This nomogram can serve as a reference for clinicians to identify high-risk neonates early and reduce the incidence of neonatal mortality.

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: chengrui350@163.com (R. Cheng), 13915509208@163.com (Z. Yang), xuyanxy2006@163.com (Y. Xu).
[1] These authors have contributed equally to this work.

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1. Introduction

Neonatal respiratory failure (NRF), a respiratory dysfunction caused by various etiologies, is a major critical condition in the neonatal intensive care unit (NICU) with high morbidity and mortality [1,2]. Large-scale epidemiologic surveys conducted in various regions of China between 2004 and 2015 revealed an incidence rate of NRF ranging from 13.2 % to 19.7 %, with a corresponding mortality rate of 15.5 %–32.1 % [3–6].

With the advancement of medical technology, the establishment of universal health insurance coverage, and ongoing enhancements in perinatal care infrastructure for neonates in China, the mortality rate of NRF has exhibited a significant decline [6,7]. Nevertheless, NRF remains the primary cause of death among critically ill neonates [8–10]. In addition, compared to the 5 % mortality rate in developed countries [11], China still has ample space for improvement. Therefore, early identification of neonates at high risk for mortality and active intervention using advanced medical resources may be indispensable in reducing death from NRF.

In 2021, Hsu et al. developed a model for predicting the mortality rate of NRF using specific criteria suitable for their study population [12]. However, considering the differences in clinical practices and medical environments across regions, it is necessary to develop a model that is tailored to the unique medical environment of mainland China. Currently, there is no predictive model that can relatively accurately forecast the risk of NRF mortality in this region, taking into account local medical practices and patient population characteristics. Therefore, we have conducted this study.

This study aims to construct a nomogram prediction model for assessing the risk of death from NRF by utilizing clinical indicators of early hospitalization and diagnostic criteria in mainland China. Our findings may offer clinicians a reference for early identification of neonates at high risk for NRF, ultimately reducing the incidence of neonatal deaths.

2. Materials and methods

2.1. Study design and participants

This retrospective study analyzed neonates treated in 21 tertiary NICUs across 13 prefecture-level cities in Jiangsu Province, China, from March 2019 to March 2022. Inclusion criteria included neonates with a confirmed diagnosis of respiratory failure, while exclusion criteria comprised patients with incomplete data or those diagnosed with chromosomal or genetic abnormalities. Using a computer-based method, one of the 21 NRF datasets was randomly selected for the external validation set. The remaining 20 datasets were randomly assigned to training and internal validation sets at a 7:3 ratio. The occurrence of death during hospitalization was used as the outcome indicator.

The conduct and reporting of this study complied with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) checklist [13]. This study was approved by the Ethics Committee of the Multicenter Clinical Research Collaborative Group on Neonatal Respiratory Failure in Jiangsu Province, China (Ethics No. 202004037-1). Due to the retrospective nature of this study with anonymized patient data, the ethics committee waived the requirement for informed consent.

2.2. Data collection and definitions

Data were retrieved from the electronic medical record systems of each participating institution, and a standardized data collection form was developed to gather the following information: (1) Maternal information: age, gestational diabetes, gestational hypertension, chorioamnionitis, placental abruption, and premature rupture of membranes (PROM); (2) Perinatal information: antenatal corticosteroid usage, methods of delivery, history of intrauterine distress, nature of amniotic fluid, 1-min Apgar score, 5-min Apgar score, neonatal resuscitation, oxygen administration, positive pressure ventilation, intubation, cardiac compressions, and pulmonary surfactant (PS) administration in the delivery room; and (3) Neonatal information: sex, gestational age, birth weight, birth weight to gestational age ratio (RBG), hypothermia, respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN), air leak, mode of first respiratory support, number of PS administrations, use of inhaled nitric oxide (INO), caffeine, vasoactive drugs, and mortality status.

In this study, NRF was defined by clinical and blood gas-confirmed hypoxemia in neonates within the first seven days of life, requiring invasive mechanical or noninvasive assisted ventilation for at least 24 h [3–6]. Clinical indicators encompassed inspiratory retraction, grunting, central cyanosis, or a respiratory rate above 60 breaths per minute. Blood gas indicators included arterial oxygen partial pressure (PaO_2) below 50 mmHg (corresponding to SpO_2 under 0.80), arterial blood pH below 7.2, and/or $PaCO_2$ above 60 mmHg. Noninvasive assisted ventilation methods encompassed continuous positive airway pressure, non-invasive positive pressure ventilation, bilevel positive airway pressure, high-flow nasal cannula, and non-invasive high-frequency oscillatory ventilation. Definitions of other variables are detailed in Supplementary Material 1.

2.3. Sample size

The sample size for developing the predictive model was determined according to the rule of having a minimum of 10 events per predictor variable [14,15]. Accordingly, the total number of deaths in the training set was at least 10 times greater than the number of predicted independent variables.

2.4. Statistical analysis

Quantitative data normality was assessed using histograms and the Kolmogorov-Smirnov test. Normally distributed data were reported as mean ± standard deviation, while skewed data were expressed as interquartile range. Categorical data were presented as frequency and percentage (%).

In the training set, the least absolute shrinkage and selection operator (LASSO) regression selected variables corresponding to the minimum value of λ as predictive factors. These variables underwent further screening and model construction through multivariate logistic regression analysis using forward stepwise, backward stepwise, and stepwise regression methods. The final nomogram prediction model was chosen based on the Akaike Information Criterion (AIC), selecting the model with the smallest AIC value.

The model performance was assessed and validated in the training set, internal validation set, and external validation set. The receiver operating characteristic (ROC) curve was plotted to evaluate the discriminative ability of the model. The area under the curve (AUC) was calculated, with an AUC>0.7 indicating good discriminative ability of the model [16]. The Youden index, positive predictive power, and negative predictive power were calculated to further evaluate the model's discriminative ability. The calibration of the prediction model was qualitatively evaluated by a calibration scatter plot, where closer proximity of predicted values to the diagonal line indicated better calibration. Additionally, the calibration of the prediction model was quantitatively evaluated by the Hosmer-Lemeshow goodness of fit test and the Brier score, with good calibration indicated by $P > 0.05$ and Brier score <0.25 [17]. The clinical relevance of the predictive model was evaluated by the decision curve analysis.

The statistical analysis was performed using SPSS version 26.0 (IBM, Armonk, NY, USA), R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and Stata version 16.0 (Stata Corporation, College Station, TX). A significance level of $P < 0.05$ indicated a statistically significant difference.

3. Results

3.1. General characteristics

The study included a training set of 3444 individuals and an internal validation set of 1470 individuals. In the training set, there were 278 deaths, while in the internal validation set, there were 128 deaths. Additionally, an external validation set of 473 individuals was included, with 27 deaths recorded. Fig. 1 illustrates the screening of the study population and the development and validation of the nomogram prediction model. The demographic characteristics of the study population are presented in Table 1.

3.2. Development of the nomogram prediction model

Lasso regression analyzed all variables, with each curve in Fig. 2A showing the coefficient change trajectory for each predictor variable. Fig. 2B highlights the minimum λ value with a vertical line, identifying 27 predictor variables with non-zero coefficients. These variables served as independent variables in constructing a multivariate logistic regression prediction model. Forward stepwise, backward stepwise, and stepwise regression methods were applied separately for variable screening and model construction. AIC values were calculated for each model, revealing that models built with backward and stepwise regression were identical and had the lowest AIC scores. Ultimately, a nomogram prediction model was developed using the eight variables with the lowest AIC values: 1-min Apgar score, birth weight, gestational age, RBG, mode of initial respiratory support, INO, antenatal corticosteroids, and vasoactive drugs. Table 2 presents the results of the multivariate logistic regression analysis. As the final model included eight predictors, the

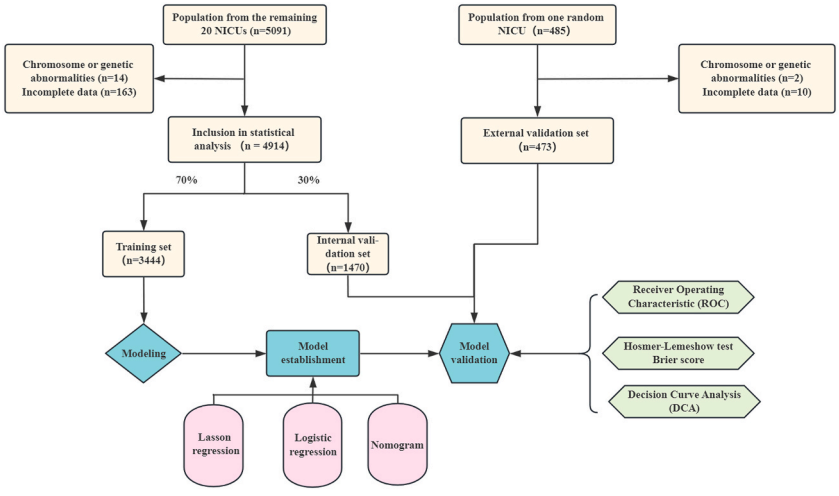

Fig. 1. The flow chart depicting the screening of the study population and the development and validation of the nomogram prediction model.

Table 1
Baseline characteristics of all patients in the training set and validation set.

Variables	Training set (n = 3444)	Internal validation set (n = 1470)	External validation set (n = 473)	*p* Value
Maternal information				
Age(weeks), mean(SD)	30.3 ± 4.9	30.2 ± 5.0	30.5 ± 4.6	0.645
Gestational diabetes, n(%)	611(17.7)	208(14.1)	58(12.3)	0.063
Gestational hypertension, n(%)	499(14.5)	212(14.4)	32(6.8)	0.04
Chorioamnionitis, n(%)	135(3.9)	57(3.9)	6(1.3)	0.069
Placental abruption, n(%)	133(3.9)	59(4.0)	9(1.9)	0.107
PROM, n(%)	328(9.5)	151(10.3)	61(12.9)	0.543
Perinatal information				
Delivery method				0.703
Natural delivery, n(%)	1140(33.1)	384(32.9)	164(34.7)	
Assisted delivery, n(%)	35(1.0)	10(0.7)	4(0.8)	
Elective cesarean section, n(%)	1476(42.9)	619(42.1)	245(51.8)	
Emergency cesarean section, n(%)	793(23)	357(24.3)	60(12.7)	
Intrauterine distress	331(9.6)	164(11.2)	43(9.1)	0.088
Amniotic fluid				0.252
Amniotic fluid III-degree turbid, or bloody amniotic fluid, n(%)	291(8.4)	135(9.2)	59(12.5)	
1-min Apgar score				0.394
<8, n(%)	1096(31.8)	498(33.9)	155(32.8)	
5-min Apgar score				0.041
<8, n(%)	513(14.9)	237(16.1)	41(8.7)	
Delivery room resuscitation, n(%)	1950(56.6)	830(56.5)	250(52.9)	0.356
Oxygen administration, n(%)[a]	984(28.6)	425(28.9)	170(35.9)	0.051
Positive pressure ventilation, n(%)[a]	670(19.5)	297(20.2)	105(22.2)	0.702
Tracheal intubation, n(%)[a]	269(7.8)	145(9.9)	44(9.3)	0.165
Cardiac compression, n(%)[a]	140(4.1)	84(5.7)	6(1.3)	<0.001
PS, n(%)[a]	39(1.1)	9(0.6)	0(0)	0.976
Antenatal corticosteroids, n(%)[c]	417(28.4)	976(28.3)	184(38.9)	0.054
Neonatal information				
Gender				0.988
Male, n(%)	2083(60.5)	869(59.1)	272(57.5)	
Female, n(%)	1361(39.5)	601(40.9)	201(42.5)	
Gestational age (weeks), mean(SD)	33.3 ± 3.7	33.3 ± 3.6	33.4 ± 3.5	0.52
Birth weight (g), mean (SD)	2086 ± 837	2090 ± 841	2012 ± 734	0.383
RBG				0.089
SGA, n (%)	193(5.6)	67(4.6)	76(16.1)	
hypothermia, n (%)	114(3.3)	51(3.5)	15(3.2)	0.73
RDS, n (%)	1867(54.2)	815(55.4)	158(33.4)	0.035
MAS, n (%)	54(1.6)	16(1.1)	11(2.3)	0.05
PPHN, n (%)	59(1.7)	22(1.5)	3(0.6)	0.506
Air leak, n (%)	56(1.6)	19(1.3)	1(0.2)	0.426
Non-invasive respiratory support, n(%)[b]	1769(51.4)	762(51.8)	269(56.9)	0.229
INO, n (%)	103(3.0)	30(2.0)	11(2.3)	0.52
PS usage times (≥2), n (%)	225(6.5)	96(6.5)	13(2.7)	0.03
Caffeine use, n (%)	1288(37.4)	559(38)	160(33.8)	0.043
Vasoactive drug use, n (%)	937(27.2)	420(28.6)	119(25.2)	0.054
Mortality, n (%)	278(8.1)	128(8.7)	27(6.0)	0.082

Note: SD, standard deviation; PROM, premature rupture of membrane. SGA, small for gestational age. RBG, the relationship between birth weight and gestational age. RDS, neonatal respiratory distress syndrome. MAS, meconium aspiration syndrome. PPHN, persistent pulmonary hypertension of the newborn. INO, inhaled nitric oxide. PS, pulmonary surfactant.

[a] Measures were taken during resuscitation in the delivery room.

[b] Respiratory support mode was adopted for the first time.

[c] Full course of treatment.

number of deaths in the training set should not be less than 80. In this study, the number of deaths in the training set was 278, meeting the sample size requirement.

In the nomogram prediction model (Fig. 3), the predictive variables for each case were assigned scores, which were then summed to obtain a total score. This total score was used to derive the probability of death during hospitalization for a case of NRF.

3.3. Model evaluation and validation

ROC curve analysis demonstrated that the AUC was 0.763 (95 % CI 0.733–0.792) for the training set, 0.733 (95 % CI 0.731–0.814) for the internal validation set, and 0.891 (95 % CI 0.815–0.967) for the external validation set (Fig. 4). All AUC values exceeded 0.7, indicating a discriminative ability of the model. The positive predictive power values for the training, internal validation, and external

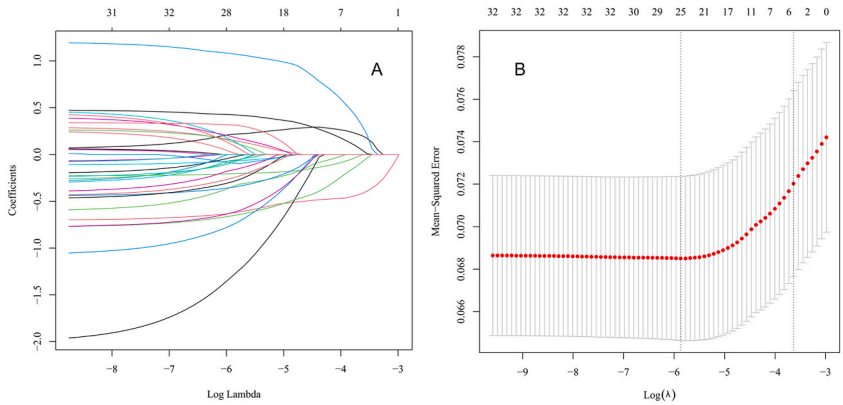

Fig. 2. Screening of variables based on LASSO regression.
(A) The variation characteristics of the coefficient of variables; (B) The results of the LASSO regression cross-validation screening variable.

Table 2
Multivariate logistic regression analysis of the predictive factors.

Variables	β value	SE value	Wald value	P value	OR value	95%CI
1-min Apgar score (4–7)	1.409	0.200	49.661	<0.001	4.090	2.764–6.052
Birth weight (1000 g–1500 g)	2.737	0.774	12.490	<0.001	15.433	3.383–70.401
Non-invasive respiratory[a]	−0.599	0.151	15.646	<0.001	0.550	0.409–0.739
INO	1.105	0.262	17.802	<0.001	3.020	1.807–5.046
Gestational age (≥37 weeks)	−0.821	0.265	9.592	0.002	0.440	0.262–0.740
Antenatal corticosteroids[b]	−0.425	0.174	5.929	0.015	0.654	0.465–0.920
Vasoactive drugs	0.332	0.144	5.293	0.021	1.394	1.050–1.849
RBG (AGA)	−0.771	0.449	2.948	0.086	0.463	0.192–1.115

Note: RBG, the relationship between birth weight and gestational age. AGA, appropriate for gestational age.
[a] Respiratory support mode was adopted for the first time.
[b] Full course of treatment.

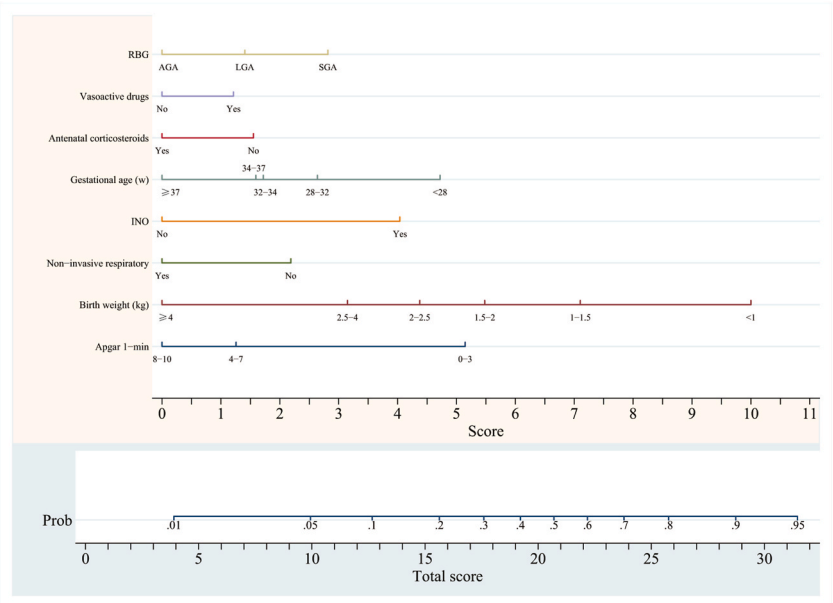

Fig. 3. A nomogram model for predicting the occurrence of death during hospitalization among neonates with respiratory failure.
(RBG, the relationship between birth weight and gestational age. INO, inhaled nitric oxide.).

validation sets were 0.725, 0.706, and 0.883, respectively. The negative predictive power values for these sets were 0.763, 0.828, and 0.778, respectively. The cutoff values of the ROC curve, calculated using Youden's Index, were 0.065, 0.059, and 0.104, respectively, for these sets.

In terms of model calibration, the predicted values for the training set, internal validation set, and external validation set were all close to the diagonal (Fig. 5). The p-values obtained from the Hosmer-Lemeshow goodness of fit test were 0.638, 0.273, and 0.253 for the respective sets, all of which exceeded 0.05. Similarly, the Brier scores for these sets were 0.066, 0.072, and 0.037, all falling below 0.25. These findings collectively suggest that the model demonstrates strong agreement between the actual and predicted incidence rates.

In terms of clinical relevance, decision curve analysis demonstrated significant net benefits for the training set, internal validation set, and external validation set. The net benefits for different threshold probabilities are presented in Fig. 6.

4. Discussion

This study is the first to develop and validate a nomogram prediction model using multicenter, large-sample data and diagnostic criteria in mainland China. The model aims to predict the risk of death in neonates with NRF and comprises eight predictive factors: 1-min Apgar score, birth weight, gestational age, RBG, mode of first respiratory support, INO, antenatal corticosteroids, and vasoactive drugs. These clinical indicators are readily obtainable in the early stages of hospitalization, enabling clinical physicians to identify high-risk neonates and allocate necessary medical resources for proactive intervention, potentially reducing the NRF mortality rate.

The timeframe of this study was set from March 2019 to March 2022, coinciding with the global pandemic of COVID-19. During this period, a series of strict isolation policies and hospital infection control measures were implemented in Mainland China. Specifically, we conducted a meticulous assessment of the risk of COVID-19 infection for all neonates admitted to the hospital. For those infants who were assessed as high-risk or suspected of infection, we implemented single-room isolation treatment and promptly transferred them to designated infectious disease hospitals for specialized treatment upon confirmation of the diagnosis. Given that the 21 medical institutions participating in this study are not designated hospitals for the treatment of COVID-19, and coupled with the strict enforcement of the aforementioned prevention and control measures, the possibility of COVID-19 infection in our study population was essentially excluded.

The Apgar score is affected by various factors, and thus the prognosis of a neonate cannot be determined solely based on a high or low score [18]. Although lower Apgar scores are associated with higher rates of neonatal mortality and morbidity, and the 5-min Apgar score is more strongly correlated with death than the 1-min Apgar score, the Apgar score cannot reliably predict individual patient outcomes [19–21]. Our prediction model included the 1-min Apgar score as a predictor, which is not contradictory. This is because the prediction model assesses the comprehensive predictive capability of all predictive factors combined, rather than the predictive effect of individual predictive factors.

Previous studies have demonstrated an inverse relationship between neonatal mortality and birth weight as well as gestational age, i.e. lower birth weight and younger gestational age correlates with higher neonatal mortality rates [20,22,23]. The same trend was observed in the present study. In our prediction model, birth weight and gestational age gradually decreased while the corresponding scores gradually increased, and the highest scores were associated with weights less than 1000 g. Thus, these factors have a greater impact on NRF mortality.

There is also a correlation between RBG and neonatal mortality. RBG categorized neonates as small for gestational age (SGA), appropriate for gestational age (AGA), or large for gestational age (LGA). Flamant et al. demonstrated that the relative risk of neonatal mortality was 2–4 times higher in SGA infants than in AGA infants irrespective of the gestational age [24]. Moreover, Chen et al. reported that among 123383 live births, the infant mortality rate was 11 per 1000 for SGA infants and 2.7 per 1000 for LGA infants [25]. Additionally, neonatal mortality was higher in LGA infants compared to AGA infants at the same gestational age [26,27]. A retrospective study of preterm infants from the Canadian Neonatal Network and Canadian Neonatal Follow-Up Network databases indicated that the risk of death in LGA infants was 1.6 times higher than in AGA infants [28]. Here, we observed a consistent trend in our NRF cohort. The scores corresponding to AGA, LGA, and SGA showed a gradual increase in our established prediction model.

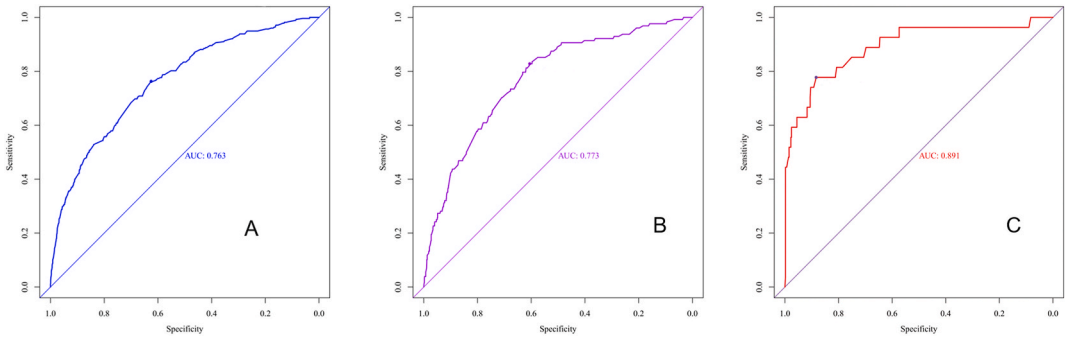

Fig. 4. Validation of the prediction model using the receiver operating characteristic (ROC) curve.
(A) Training set; (B) Internal validation set; (C) External validation set. (AUC, the area under the ROC curve.)

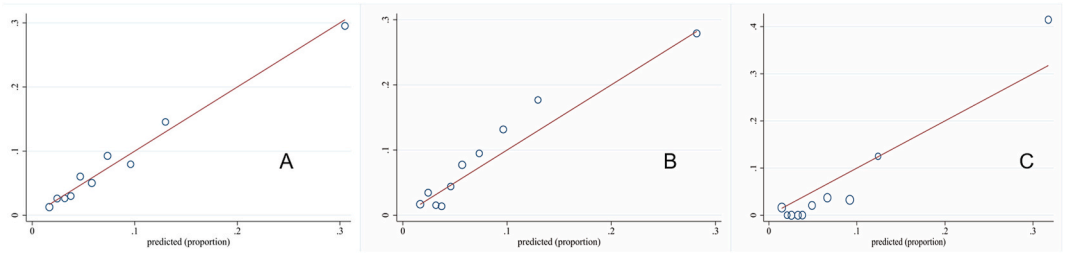

Fig. 5. The calibration scatter plot of the predictive model.
(A) Training set; (B) Internal validation set; (C) External validation set.

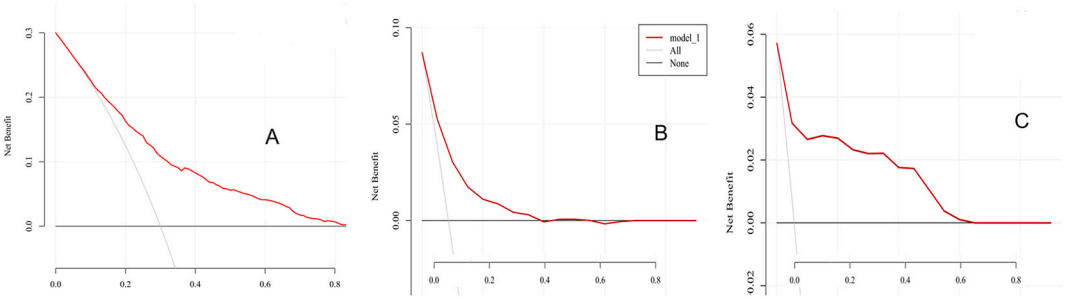

Fig. 6. Decision curve analysis of the predictive model.
(A) Training set; (B) Internal validation set; (C) External validation set.

Invasive respiratory support, INO, and vasoactive drugs play a beneficial role in managing critically ill neonates. Nonetheless, our prediction model indicated higher scores for these factors compared to noninvasive respiratory support, absence of INO use, and absence of vasoactive drug use. However, it is important to note that this does not imply that the use of invasive ventilatory support, INO, and vasoactive drugs is a risk factor for death in NRF and should therefore be minimized or avoided. Rather, it suggests that neonates who are hospitalized early with invasive respiratory support, INO, and vasoactive drugs are typically in a more critical condition, and consequently, are at a higher risk of death.

The prenatal application of glucocorticoid therapy to pregnant women has improved the survival of preterm infants by mimicking physiologic stress levels [29]. In a retrospective analysis of a national cohort study in Canada, involving 43456 preterm infants born at less than 34 weeks of gestational age, it was found that prenatal glucocorticoids significantly reduced the risk of preterm infant mortality [30]. Similarly, a retrospective study conducted at 87 tertiary care centers of the Japanese Neonatal Network, which included 11607 preterm infants, showed that prenatal use of glucocorticoids significantly enhanced the survival rate of preterm infants [31]. Consistently, our study in the NRF cohort also demonstrated that prenatal use of hormones reduced the risk of NRF deaths.

This study faces several limitations. Firstly, as a multicenter, retrospective study, internal bias is inherent. Secondly, data collection relied on various electronic medical record systems, leading to difficulties due to system disparities. Some systems could not retrieve laboratory data of discharged patients or ventilator settings, resulting in missing important variables for model construction. Future studies should address these data collection challenges and evaluate more potential indicators, including laboratory test results and ventilator settings, to develop a more accurate prediction model and reduce neonatal mortality. Thirdly, the exclusion of patients with chromosomal and genetic abnormalities is notable, as routine screening for these conditions was not conducted by the collaborating team, potentially overlooking some patients. Finally, data from Jiangsu Province, China—a region with ample healthcare resources and economic prosperity—were used, which may limit the model's applicability to other regions.

In conclusion, we have successfully developed a nomogram model for predicting the risk of death in neonates with NRF. This nomogram provides clinicians with a simple and intuitive tool for early detection and identification of high-risk neonates, which could be crucial in reducing the high mortality associated with NRF.

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Data availability statement

The data supporting this article will be made available upon reasonable request to the corresponding author.

Ethical standards

This study was approved by the Ethics Committee of the Multicenter Clinical Research Collaborative Group on Neonatal Respiratory Failure in Jiangsu Province, China (Ethics No. 202004037-1). As this was a retrospective study, and patients were anonymized during data collection, informed consent was waived by the ethics committee.

CRediT authorship contribution statement

Bo Wang: Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Yue Wu:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation. **Jie Shao:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation. **Rui Cheng:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Zuming Yang:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Yan Xu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Rui Cheng reports financial support was provided by Nanjing Medical University Special Disease Cohort Foundation. Rui Cheng reports financial support was provided by National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37437.

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