Heliyon 9 (2023) e18964

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

A nomogram for predicting the risk of Bronchopulmonary dysplasia in premature infants

Xian Shen [a], Nishant Patel [b], Wen Zhu [a], Xu Chen [a], Keyu Lu [a], Rui Cheng [a], Xuming Mo [b,*]

[a] Department of Neonatology, Children's Hospital of Nanjing Medical University, Nanjing, 210008, China
[b] Department of Cardiothoracic Surgery, Children's Hospital of Nanjing Medical University, Nanjing, 210008, China

ARTICLE INFO

Keywords:
Bronchopulmonary dysplasia
Premature infants
Risk identification
Prediction
Nomogram

ABSTRACT

Background: Bronchopulmonary dysplasia (BPD) is a prevalent and critical complication among premature infants, with potentially long-lasting adverse effetcs. The present study aimed to establish a nomogram model to predict the risk of BPD in premature infants born at <32 weeks gestational age.

Methods: A retrospective single-center study was conducted on premature infants admitted to the neonatal intensive care unit (NICU) of the Children's Hospital of Nanjing Medical University from January 2018 to December 2020. Data were collected from clinical medical records, including the perinatal data and the critical information after birth. Clinical parameters and features were analyzed using univariate and multivariate logistic regression. A nomogram based on clinical data was established and validated using bootstrapping samples. The specificity and sensitivity of the nomogram were estimated using the receiver operating characteristic (ROC) based area under the curve (AUC).

Results: A total of 542 premature babies were included, and 152 infants (28.04%) were diagnosed with BPD. Birth weight, cesarean delivery, invasive/non-invasive ventilation at day 7 and 14 were identified as significant factors ($p < 0.05$) using univariate and the multivariate logistic regression analysis, and were entered into a nomogram. The calibration curve for BPD probability demonstrated a favorable concurrence between actual probability and predicted ability of the BPD nomogram. The nomogram showed potential differentiation, with an AUC of 0.925, 89.90% sensitivity, 76.71% specificity, and 86.35% accuracy.

Conclusion: The nomogram developed in this study provides a straightforward tool to predict the probability of BPD and assist clinicians in optimizing treatment regimens for premature infants born at <32 weeks gestational age. This study highlights the importance of identifying and monitoring significant clinical factors associated with BPD in premature infants to improve clinical outcomes.

1. Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease and a significant complication of premature infants. Despite advances

* Corresponding author.
E-mail address: mohsuming15@njmu.edu.cn (X. Mo).

https://doi.org/10.1016/j.heliyon.2023.e18964
Received 20 October 2022; Received in revised form 11 July 2023; Accepted 3 August 2023
Available online 9 August 2023

in perinatal medicine, BPD continues to be a rising concern in extremely and very preterm infants [1]. BPD incidence in preterm infants born at < 29 weeks gestational age (GA) is as high as 45% [2]. BPD affects not only lung function but also systemic health, resulting in lifelong effects on quality of life and health outcomes [3,4]. Studies have shown that surviving premature infants with BPD have an increased risk of short-term complications and sequelae such as pulmonary hypertension, growth retardation, and readmission, as well as long-term effects such as asthma, airway obstructive disease, and cardiovascular sequelae [5]. Therefore, BPD seriously affects and threatens the life quality and safety of premature infants, also poses a significant burden on the families and communities.

Currently, there is no specific and effective treatment for BPD. Therefore, preventing its occurrence is of utmost importance. Developing a simple, easy-to-use, and accurate predictive model for premature infants prone to BPD can help clinicians adjust treatment strategies timely and improve prognosis. Previous studies have developed predictive models for onset disease, the severity of onset disease, and the occurrence of childhood respiratory diseases after BPD [6–8]. However, these models have varied in the factors they include. Some models have included chest X-ray or computed tomography (CT) imaging scores, which are subjective and not standardized between centers [9,10]. Other models have introduced blood inflammation-based specific indicators [11], which are not readily available for routine clinical detection and increase the economic burden. In addition, most prediction models are based on the European and American populations [6], and their applicability to Asian populations needs further investigation.

Therefore, based on three-year dataset from a tertiary NICU center in China, our study aims to construct a BPD nomogram prediction model based on common parameters that are readily available in prenatal, perinatal, and postpartum clinics. Such a model could assist clinicians in optimizing treatment regimens for premature infants born at <32 weeks gestational age and improve clinical outcomes.

2. Methods

2.1. Study design

A retrospective single-center study was carried out in the NICU of the Children's Hospital of Nanjing Medical University. Infants admitted to the NICU from January 01, 2018, to December 31, 2020, were included in the study if they met the following inclusion criteria: (1) born at <32 weeks GA; (2) had a hospital stay≥ 28 days. Exclusion criteria were: (1) congenital abnormalities or inborn errors; (2) suspected genetic metabolic diseases or chromosomal abnormalities; (3) infection at admission; (4) requirement of surgery during the hospital stay; (5) missing/incomplete clinical data such as maternal pregnancy and childbirth-related information.

2.2. Clinical data collection

Hospital records were used to collect data on the following: (1) infants' general condition, including GA, birth weight (BW), gender, mode of delivery, twins and multiple births, 5min Apgar Score ≤7, and resuscitation at birth; (2) maternal conditions, including premature rupture of membranes (PROM) > 18 h, gestational diabetes, gestational hypertension, antenatal corticosteroids use and ages of parents; (3) clinical manifestations and complications, including neonatal respiratory distress syndrome (NRDS), pulmonary hemorrhage, pneumothorax, pneumonia and/or sepsis, patent ductus arteriosus (PDA), hemodynamically significant PDA (hsPDA), periventricular/intraventricular hemorrhage (PVH/IVH), retinopathy of prematurity (ROP), necrotizing entrocolitis (NEC); (4) treatment strategies, including pulmonary surfactant therapy, invasive and non-invasive ventilation, duration of invasive ventilation, invasive/non-invasive ventilation at day 7 and 14.

GA was defined as the number of weeks between the first day of the mother's last menstrual cycle and the day of birth. NRDS was characterized as the onset of respiratory distress that cannot be addressed through other causes as determined by a chest x-ray and other medical tests. Pneumonia was determined based on clinical indicators and thoracic imaging data. Clinical manifestations, positive blood tests and inflammatory markers were used to diagnose sepsis. Within the first 1 week of life, a 2D color Doppler screening was used to confirm PDA. The echocardiogram was repeated according to clinical need. A diagnosis of hs-PDA met the relevant clinical features such as deterioration of respiratory system, low diastolic or mean blood pressure, unexplained acidosis, feeding intolerance, and one of the criteria from echocardiographic: ≥1.5 mm ductal diameter, >1.5 left atrium/aorta ratio, 1.5 peak velocity of ductus arteriosus. According to the modified criteria of Bell, NEC was diagnosed. Meanwhile, the international classification of ROP was used to identify ROP. PVH/IVH was determined by the ultrasound of the cranial at a series of weekly check-ups after birth.

In our NICU, the diagnosis of BPD was established according to the criteria outlined by the National Institute of Child Health and Human Development (NICHD) criterion established in 2001 [12]. The diagnostic criteria included: (1) treatment with supplemental oxygen (FiO2 > 0.21) for a minimum duration of 28 days; (2) worsening or persistent respiratory insufficiency; and (3) exclusion of other respiratory support-dependent conditions such as pneumothorax, severe congenital cardiopathy, pleural effusion, among others. The clinical grading of BPD was determined by evaluating the infants' respiratory support at 36 weeks postmenstrual age (PMA) or at discharge. The severity of BPD was classified as mild (no supplemental oxygen required), moderate (<0.3 level of FiO2), or severe (≥0.3 level of FiO2 and/or mechanical ventilation or positive pressure ventilation). This standardized approach allowed for consistent and accurate diagnosis of BPD in our NICU, which is crucial for appropriate management and follow-up of affected infants.

2.3. Nomogram development and statistics analysis

In our study, variables that followed a normal distribution were expressed as mean ± standard deviation and analyzed using an independent *t*-test. For variables that did not follow a normal distribution, median (IQR) was used, and a non-parametric Mann-

Whitney test was conducted. For categorical variables, both the $\chi 2$ test and Fisher's exact test were employed, and percentages were reported. Univariate logistic regression was conducted to examine each variable, and only statistically significant variables ($p < 0.05$) were selected for further multivariate logistic regression analysis. The Enter approach was used to calculate the adjusted odds ratio (OR) and the corresponding 95% confidence interval (CI) in the multivariate analysis. Based on the significant risk factors identified from the multivariate analysis, we constructed a nomogram to predict the probability of BPD occurrence. To evaluate the performance of the nomogram, we conducted calibration and discrimination analyses. The calibration plot was used to visually compare the actual and predicted probabilities of BPD, while 1000 bootstraps resamples were utilized for internal validation. The discriminative capability of the nomogram was measured using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. We defined a statistically significant difference as $p < 0.05$. SPSS 22.0 (IBM Inc., Chicago, USA) and R 3.1.2 (Rstudio Co., Boston, USA) with the rms statistical packages were used for statistical analyses and graphics.

3. Results

3.1. Demographic characteristics of the study

Our study included a cohort of 554 premature infants born at <32 weeks GA, of which 8 infants had congenital heart disease and/or surgery intervention, and 4 infants abandoned therapy or died before PMA of 36 weeks. Therefore, 542 premature infants were ultimately included in our analysis, of which 152 premature infants were diagnosed with BPD and 390 infants were without BPD. The cohort included 245 (45.2%) females and 297 (54.8%) males, with a median GA of 29.71 weeks and a mean BW of 1326.12 g. Of the mothers, 56.5% were given the complete doses of antenatal corticosteroids. Among the infants with BPD, 77 (50.7%), 43 (28.3%), and 32 (21.1%) had mild, moderate, and severe BPD, respectively.

Table 1 displays the demographic characteristics of premature infants categorized into two groups, BPD and non-BPD. The BPD group was observed to have smaller weight and less gestational age than non-BPD patients [1112.24 ± 239.97 g vs 1409.47 ± 254.58 g ($p < 0.001$), 28.71 (27.57, 29.71) weeks vs 30.29 (29.14, 31.14) weeks ($p < 0.001$), respectively]. Additionally, the proportion of cesarean delivery was significantly lower in the BPD group than in the non-BPD group (41.4% vs. 56.2%, $p = 0.002$). Patients who developed BPD were also found to have a higher incidence of 5min Apgar Score ≤7 (13.8% vs 3.6%, $p < 0.001$), and elevated incidence of resuscitation at birth (18.4% vs 8.5%, $p < 0.001$). Furthermore, surfactant administration (51.3% vs 39.7%, $p = 0.015$) and hs-PDA (15.1% vs 5.6%, $p < 0.001$) were also more prevalent in the BPD group. Rates of both invasive and non-invasive ventilations were elevated in the BPD group (68.4% vs 32.6%, $p < 0.001$, 94.1% vs 66.7%, $p < 0.001$, discretely), and the duration of invasive ventilation was also longer [84 (0, 236.25) h vs 0 (0,39.25) h, $p < 0.001$]. Moreover, the BPD group had a higer probability of invasive/non-

Table 1
Clinical characteristics of the prematures and their parents by BPD status.

	Non-BPD group (n = 390)	BPD group (n = 152)	*P*
Gestational age (weeks), median (IQR)	30.29 (29.14, 31.14)	28.71 (27.57, 29.71)	<0.001
Birth weight (g), mean (SD)	1409.47 (254.58)	1112.24 (239.97)	<0.001
Male,n (%)	207 (53.1)	90 (59.2)	0.197
Twins and multiple births,n (%)	131 (33.6)	40 (26.3)	0.102
Cesarean delivery,n (%)	219 (56.2)	63 (41.4)	0.002
5min Apgar Score≤7,n (%)	14 (3.6)	21 (13.8)	<0.001
Resuscitation at birth,n (%)	33 (8.5)	28 (18.4)	0.001
Age of father, mean (SD)	32.32 (5.43)	32.81 (6.1)	0.364
Age of mother, mean (SD)	30.52 (4.8)	31.12 (5.1)	0.206
Complete cause of antenatal corticosteroid,n (%)	228 (58.5)	78 (51.3)	0.132
PROM>18 h,n (%)	88 (22.6)	37 (24.3)	0.659
Gestational diabetes,n (%)	39 (10.0)	18 (11.8)	0.530
Gestational hypertention,n (%)	64 (16.4)	26 (17.2)	0.821
NRDS,n (%)	206 (52.8)	83 (54.6)	0.708
Pulmonary hemorrhage, n (%)	8 (2.1)	7 (4.6)	0.100
Pneumothorax,n (%)	1 (0.3)	1 (0.7)	0.489
Pneumonia and/or sepsis,n (%)	141 (36.2)	60 (39.5)	0.472
PDA,n (%)	219 (56.2)	94 (61.8)	0.228
hs-PDA,n (%)	22 (5.6)	23 (15.1)	<0.001
PVH-IVH(≥II),n (%)	371 (95.1)	140 (92.1)	0.173
ROP(≥2),n (%)	51 (13.1)	17 (11.2)	0.550
NEC (≥IB),n (%)	90 (23.1)	34 (22.4)	0.860
PS therapy, n (%)	155 (39.7)	78 (51.3)	0.015
Non invasive ventilation,n (%)	260 (66.7)	143 (94.1)	<0.001
Invasive ventilation (%)	127 (32.6)	104 (68.4)	<0.001
Ventilation at day 7,n (%)	153 (39.2)	144 (94.7)	<0.001
Ventilation at day 14,n (%)	68 (17.4)	128 (84.2)	<0.001
Duration of invasive ventilation (h), median (IQR)	0 (0,39.25)	84 (0, 236.25)	<0.001

PROM, premature rupture of membranes; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; hs-PDA, hemodynamically significant PDA; PVH-IVH, periventricular/intraventricular hemorrhage; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; PS, pulmonary surfactant; Ventilation at day 7 = Invasive/Non-invasive ventilation at day 7; Ventilation at day 14 = Invasive/Non-invasive ventilation at day 14.

invasive ventilation at day 7 and day 14 [94.7% vs 39.2%, $p < 0.001$, 84.2% vs 17.4%, $p < 0.001$]. The study observed no significant differences between the two groups with respect to gender, twins and multiple births, ages of parents, complete cause of antenatal corticosteroid, PROM>18 h, gestational diabetes, and gestational hypertension. There were no significant differences in the incidence of NRDS, pulmonary hemorrhage, pneumothorax, pneumonia and/or sepsis, PDA, PVH-IVH, ROP and NEC.

4. Risk factors in preterm infants with BPD

In our study, we utilized univariate regression to determine the differences between premature infants with and without BPD. Twelve variables were found to be significantly different between the two groups, including: GA, BW, cesarean delivery, 5min Apgar Score ≤7, resuscitation at birth, pulmonary surfactant therapy, hsPDA, invasive and non-invasive ventilation, duration of invasive ventilation, invasive/non-invasive ventilation at day 7 and 14 ($p < 0.05$). Subsequently, we conducted a multivariable logistic regression analysis and identified birth weight (OR = 0.997, 95% CI: 0.995–0.998), cesarean delivery (OR = 0.441, 95% CI: 0.243–0.801), invasive/non-invasive ventilation at day 7 (OR = 6.004, 95% CI: 2.515–14.334) and invasive/non-invasive ventilation at day 14(OR = 7.099, 95% CI: 3.802–13.255) as independent risk factors associated with BPD (Table 2). These findings suggest that careful management of ventilation and delivery mode may be important in reducing the incidence of BPD in premature infants.

4.1. Nomogram construction

A nomogram was constructed based on the significant risk factors identified by multivariate regression analysis to predict the development of BPD in premature infants (Fig. 1). The BW was found to be the most significant risk factor for BPD, followed by invasive/non-invasive ventilation at day 14, invasive/non-invasive ventilation at day 7 and cesarean delivery. By combining the points assigned to each variable, the nomogram provides a tool to estimate the likelihood of BPD in a given infant. For example, a premature infant with vaginal delivery and a BW of 800 g requiring ongoing invasive or non-invasive ventilation at day 7 and 14 would have approximately a 90% probability of developing BPD. This nomogram may help clinicians to identify infants at high risk for BPD and implement preventive measures accordingly.

4.2. Validation and efficacy of nomogram

To evaluate the calibration of BPD, a calibration curve was used. The results showed a high level of consistency between the predicted probability and the actual probability of BPD, as demonstrated by the curve (Fig. 2A). For internal validation, the nomogram was applied to 1000 bootstrapping resamples, which demonstrated high prediction accuracy. Furthermore, ROC analysis was utilized to assess prediction efficiency of the nomogram for BPD (Fig. 2B), and the results showed an AUC value of 0.925 (95% CI: 0.902–0.948) on the ROC curve, with high sensitivity (89.90%), specificity (76.71%) and accuracy (86.35%). Thus, the nomogram model, which incorporated four variables, demonstrated superior predictive ability for BPD compared to individual variables, indicating its reliable performance in clinical settings.

5. Discussion

BPD is a chronic disease that results from multiple factors, including genetic, prenatal or postnatal influences [13–17]. Despite extensive research, the pathogenesis of BPD remains incompletely understood, although it is believed to arise from lung immaturity, infection, inflammation, oxygen toxicity, mechanical ventilation. Abnormal repair following injury is also thought to contribute to the development of BPD [13]. Unfortunately, there are currently no effective and specific treatments available for BPD. Therefore,

Table 2
Univariate and multivariate logistic regression for analyzing the risk factors for BPD.

Characteristic	Univariate			Multivariate		
	OR	95%CI	*P*	OR	95%CI	*P*
Gestational age	0.515	0.446–0.596	<0.001	0.997	0.786–1.265	0.978
Birth weight	0.995	0.994–0.996	<0.001	0.997	0.995–0.998	<0.001
Cesarean delivery	0.553	0.378–.808	0.002	0.441	0.243–0.801	0.007
5min Apgar Score ≤7	4.305	2.128–8.712	<0.001	1.945	0.656–5.767	0.230
Resuscitation at birth	2.436	1.415–4.195	0.001	1.368	0.562–3.328	0.490
Pulmonary surfactant therapy	1.598	1.096–2.330	0.015	0.629	0.325–1.216	0.168
hs-PDA,n (%)	2.982	1.608–5.533	0.001	1.022	0.411–2.543	0.963
Invasive ventilation	4.487	3.001–6.709	<0.001	1.117	0.533–2.341	0.769
Non-invasive ventilation	7.944	3.923–16.090	<0.001	2.115	0.813–5.501	0.125
Ventilation at day 7	27.882	13.298–58.462	<0.001	6.004	2.515–14.334	<0.001
Ventilation at day 14	25.255	15.189–41.991	<0.001	7.099	3.802–13.255	<0.001
Duration of invasive ventilation	1.009	1.007–1.011	<0.001	1.002	0.999–1.005	0.118

hs-PDA, hemodynamically significant PDA; Ventilation at day 7 = Invasive/Non-invasive ventilation at day 7; Ventilation at day 14 = Invasive/Non-invasive ventilation at day 14.

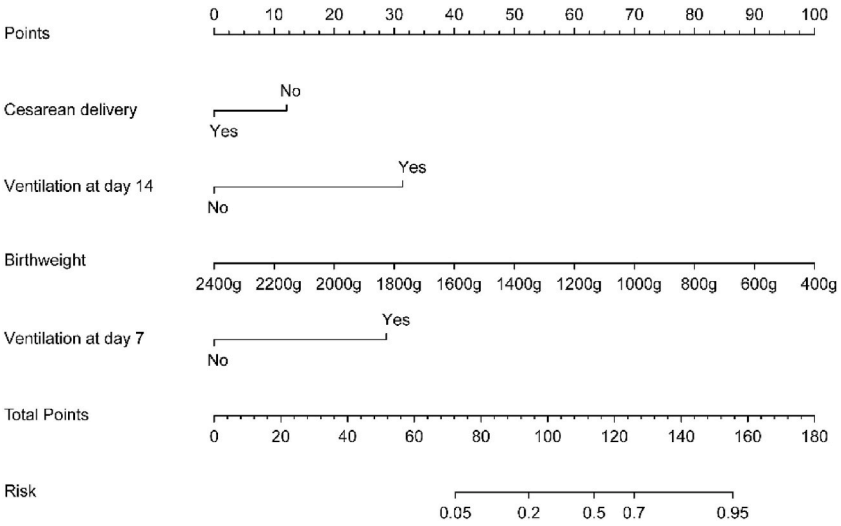

Fig. 1. The nomogram of BPD in premature infants. The value of each variable was given a score on the point scale axis. A total score could be calculated by summing every single score. The probability of BPD in premature infants will be estimated easily, by projecting the total score to the lower total point scale. Ventilation at day 7 = Invasive/Non-invasive ventilation at day 7; Ventilation at day 14 = Invasive/Non-invasive ventilation at day 14.

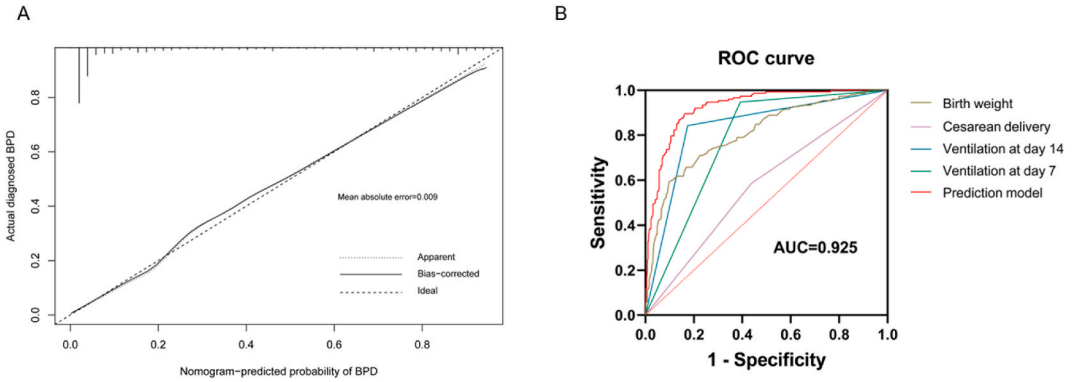

Fig. 2. Calibration plot and ROC curves for the nomogram. (A) The x-axis represents the nomogram-predicted probability and the y-axis represents the diagnosed BPD. Perfect prediction would correspond to the 45° dashed line. The dotted line represents the entire cohort (n = 542) and the solid line is bias-corrected by bootstrapping (B = 1000 repetitions), indicating observed nomogram performance. (B) The prediction nomogram model for BPD includes the variables: birth weight, cesarean delivery, ventilation at day 7 and 14. The AUC, specificity, and sensitivity for the nomogram model are higher than any of the four included risk factors alone. Ventilation at day 7 = Invasive/Non-invasive ventilation at day 7; Ventilation at day 14 = Invasive/Non-invasive ventilation at day 14.

accurate prediction of BPD in the early postnatal period is of great clinical significance, as it could acilitate the optimization of treatment plans and enable the adoption of active prevention strategies.

Our study was a retrospective analysis that examined data collected over a three-year from a single center, including preterm infants bore at < 32 weeks GA. We found that the incidence of 5 min Apgar Score≤7 and resuscitation at birth decreased significantly in the non-BPD group, whih had a higher cesarean section rate compared to the BPD group. Multivariate regression analysis demonstrated that cesarean section was protective factor against BPD, a relationship that has not been clearly reported in previous studies. Our findings suggest that if the mother has complications or the fetal intrauterine condition is unstable, a cesarean section may reduce the need for resuscitation in the delivery room, thereby decreasing the risk of asphyxia-related complications and improving the overall stability of premature infants in the early postnatal period [18]. This protective effect of cesarean section has been reported in previous studies as well, such as Tucker et al. [19] who found that extremely preterm infants with breech at 23–25 weeks of gestation had a relatively higher survival rate when delivered by cesarean section. Our study provides further insights into the potential benefits of cesarean section in improving outcomes for preterm infants, particularly with respect to reducing the risk of developing BPD.

PDA has been identified as a risk factor for BPD in previous studies [11,20], particularly in cases of hs-PDA. hs-PDA leads to changes in the hemodynamics of the heart and systemic circulation, causing pulmonary edema and increasing the likelihood of pulmonary hemorrhage, which can worsen lung compliance and injury [11]. In our study, hs-PDA was found to be significantly more common in

BPD group, and the probability of pulmonary hemorrhage was also elevated, consistent with previous studies. However, while some studies suggest a causal relationship between PDA and BPD [21], this has not yet been proven conclusively [22,23]. In our study, hs-PDA was identified as a risk factor BPD by univariate analysis, but not by multivariate regression analysis, possibly due to the sample size of hs-PDA in our study. While our findings support close monitoring of children with PDA, further evaluation and verification of the relationship between PDA and BPD in larger cohorts is warranted.

The risk factors for BPD in preterm infants are multifactorial and complex. In our study, we found the rate and duration of invasive mechanical ventilation in BPD group were significantly higher than non-BPD group, which is consistent with the previous research [11]. The use of invasive mechanical ventilation is associated with an increased risk of BPD [24–27], due to the pressure and volume injury caused by excessive stretching of lung tissue [28]. Multivariate regression analysis identified invasive/non-invasive ventilation at day 7 and 14 as independent risk factors for BPD, consistent with the study by Daniela et al. [7]. Although non-invasive ventilation is considered more beneficial for lung protection than invasive mechanical ventilation, both forms of ventilation should be used with caution, and positive pressure breathing support should be withdrawn as soon as possible to minimize lung damage. Our findings highlight the importance of timely and dynamic assessment of the condition of premature infants with ventilation and emphasize the need for individualized ventilation strategies to reduce the risk of BPD.

Eestablishing a predictive model that can accurately identify high-risk premature infants and reveal independent influencing factors of BPD is critical for clinical decision-making and management. In this study, we developed a nomogram for predicting the risk of BPD in preterm infants, utilizing independent risk factors for BPD. The nomogram was built based on easily obtained clinical indicators, including birth weight, cesarean delivery, invasive/non-invasive ventilation at day 7 and 14. The model's high predictive accuracy and simplicity make it an important tool for clinicians in a wide range of clinical settings, without adding to the burden of clinicians and children. Moreover, We intend to validate the nomogram prediction model with future prospective studies, further confirming its potential clinical significance in improving the quality of care for premature infants.

Our study has certain limitations that should be acknowledged. Firstly, the exclusion of infants who abandoned therapy or died before 36 weeks of PMA, may have resulted in incomplete and biased data. Secondly, our study was conducted retrospectively in a single center, which may limit the generalizability of our findings. Further studies with larger, multicenter infant cohorts are needed to validate the applicability of our model.

In conclusion, our study developed a nomogram prediction model based on independent risk factors for BPD, which demonstrated promising predictive performance. Our nomogram model is straightforward and easy to apply, offering a valuable tool for clinical prediction of BPD and optimization of treatment strategies for neonatology specialists. We believe that this prediction model has the potential to assist neonatology specialists in the early identification of newborns at risk for BPD, thus lowering the incidence of BPD and enhancing outcomes for premature infants.

Ethics statement

The ethics committee of the Children's Hospital of Nanjing Medical University approved the study and informed consent was waived due to the retrospective nature of the study (approval number: 202112135-1).

Funding

This study was supported by the Women and Children Health Program from Jiangsu Province (FYX202028), Jiangsu Commission of Health Program (F2020202) and the National Natural Science Foundation of China (82171705).

Author contribution statement

X Shen and X Mo conceived and designed the experiments;
X Shen, N Patel, W Zhu, X Chen and K Lu performed the experiments;
X Shen, N Patel, W Zhu analyzed and interpreted the data;
X Shen, N Patel, W Zhu, X Chen, K Lu and R Cheng contributed reagents, materials, analysis tools or data;
X Shen and X Mo wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the neonates participated in the study.

References

[1] K. Lui, S.K. Lee, S. Kusuda, M. Adams, M. Vento, B. Reichman, B.A. Darlow, L. Lehtonen, N. Modi, M. Norman, S. Hakansson, D. Bassler, F. Rusconi, A. Lodha, J. Yang, P.S. Shah, Trends in outcomes for neonates born very preterm and very low birth weight in 11 high-income countries, J. Pediatr. 215 (2019) 32–40, https://doi.org/10.1016/j.jpeds.2019.08.020.

[2] B.J. Stoll, N.I. Hansen, E.F. Bell, M.C. Walsh, W.A. Carlo, S. Shankaran, A.R. Laptook, P.J. Sanchez, K.P. Van Meurs, M. Wyckoff, A. Das, E.C. Hale, M.B. Ball, N. S. Newman, K. Schibler, B.B. Poindexter, K.A. Kennedy, C.M. Cotten, K.L. Watterberg, C.T. D'Angio, S.B. Demauro, W.E. Truog, U. Devaskar, R.D. Higgins, Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012, JAMA, J. Am. Med. Assoc. 314 (2015) 1039–1051, https://doi.org/10.1001/jama.2015.10244.

[3] A. Bhandari, H.B. Panitch, Pulmonary outcomes in bronchopulmonary dysplasia, Semin. Perinatol. 30 (2006) 219–226, https://doi.org/10.1053/j.semperi.2006.05.009.

[4] L.M. Davidson, S.K. Berkelhamer, Bronchopulmonary dysplasia: chronic lung disease of infancy and long-term pulmonary outcomes, J. Clin. Med. 6 (2017), https://doi.org/10.3390/jcm6010004.

[5] S.J. Cassady, A. Lasso-Pirot, J. Deepak, Phenotypes of bronchopulmonary dysplasia in adults, Chest 158 (2020) 2074–2081, https://doi.org/10.1016/j.chest.2020.05.553.

[6] M.M. Laughon, J.C. Langer, C.L. Bose, P.B. Smith, N. Ambalavanan, K.A. Kennedy, B.J. Stoll, S. Buchter, A.R. Laptook, R.A. Ehrenkranz, C.M. Cotten, D. E. Wilson-Costello, S. Shankaran, K.P. Van Meurs, A.S. Davis, M.G. Gantz, N.N. Finer, B.A. Yoder, R.G. Faix, W.A. Carlo, K.R. Schibler, N.S. Newman, W. Rich, A. Das, R.D. Higgins, M.C. Walsh, Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants, Am. J. Respir. Crit. Care Med. 183 (2011) 1715–1722, https://doi.org/10.1164/rccm.201101-0055OC.

[7] D. Valenzuela-Stutman, G. Marshall, J.L. Tapia, G. Mariani, A. Bancalari, A. Gonzalez, Bronchopulmonary dysplasia: risk prediction models for very-low- birth-weight infants, J. Perinatol. 39 (2019) 1275–1281, https://doi.org/10.1038/s41372-019-0430-x.

[8] L.A. Morrow, B.D. Wagner, D.A. Ingram, B.B. Poindexter, K. Schibler, C.M. Cotten, J. Dagle, M.K. Sontag, P.M. Mourani, S.H. Abman, Antenatal determinants of bronchopulmonary dysplasia and late respiratory disease in preterm infants, Am. J. Respir. Crit. Care Med. 196 (2017) 364–374, https://doi.org/10.1164/rccm.201612-2414OC.

[9] B. Yuksel, A. Greenough, J. Karani, Prediction of chronic lung disease from the chest radiograph appearance at seven days of age, Acta Paediatr. 82 (1993) 944–947, https://doi.org/10.1111/j.1651-2227.1993.tb12605.x.

[10] M. Ochiai, S. Hikino, H. Yabuuchi, H. Nakayama, K. Sato, S. Ohga, T. Hara, A new scoring system for computed tomography of the chest for assessing the clinical status of bronchopulmonary dysplasia, J. Pediatr. 152 (90–95) (2008) 91–95, https://doi.org/10.1016/j.jpeds.2007.05.043.

[11] L. Ding, H. Wang, H. Geng, N. Cui, F. Huang, X. Zhu, X. Zhu, Prediction of bronchopulmonary dysplasia in preterm infants using postnatal risk factors, Front. Pediatr. 8 (2020) 349, https://doi.org/10.3389/fped.2020.00349.

[12] A.H. Jobe, E. Bancalari, Bronchopulmonary dysplasia, Am. J. Respir. Crit. Care Med. 163 (2001) 1723–1729, https://doi.org/10.1164/ajrccm.163.7.2011060.

[13] V.V. Shukla, N. Ambalavanan, Recent advances in bronchopulmonary dysplasia, Indian J. Pediatr. 88 (2021) 690–695, https://doi.org/10.1007/s12098-021-03766-w.

[14] N. Ambalavanan, C.M. Cotten, G.P. Page, W.A. Carlo, J.C. Murray, S. Bhattacharya, T.J. Mariani, A.C. Cuna, O.M. Faye-Petersen, D. Kelly, R.D. Higgins, Integrated genomic analyses in bronchopulmonary dysplasia, J. Pediatr. 166 (2015) 531–537, https://doi.org/10.1016/j.jpeds.2014.09.052.

[15] C.V. Lal, N. Ambalavanan, Genetic predisposition to bronchopulmonary dysplasia, Semin. Perinatol. 39 (2015) 584–591, https://doi.org/10.1053/j.semperi.2015.09.004.

[16] N. Ambalavanan, K.P. Van Meurs, R. Perritt, W.A. Carlo, R.A. Ehrenkranz, D.K. Stevenson, J.A. Lemons, W.K. Poole, R.D. Higgins, Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure, J. Perinatol. 28 (2008) 420–426, https://doi.org/10.1038/jp.2008.18.

[17] L. Eriksson, B. Haglund, V. Odlind, M. Altman, U. Ewald, H. Kieler, Perinatal conditions related to growth restriction and inflammation are associated with an increased risk of bronchopulmonary dysplasia, Acta Paediatr. 104 (2015) 259–263, https://doi.org/10.1111/apa.12888.

[18] L. Gagliardi, R. Bellu, G. Lista, R. Zanini, Do differences in delivery room intubation explain different rates of bronchopulmonary dysplasia between hospitals? Arch. Dis. Child. Fetal Neonatal Ed. 96 (2011) F30–F35, https://doi.org/10.1136/adc.2010.183905.

[19] E.B. Tucker, F. Mckenzie, M. Macheras, S.K. Srinivas, S.A. Lorch, Morbidity and mortality associated with mode of delivery for breech periviable deliveries, Am. J. Obstet. Gynecol. 213 (2015) 70–71, https://doi.org/10.1016/j.ajog.2015.03.002.

[20] R.I. Clyman, The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia, Semin. Perinatol. 37 (2013) 102–107, https://doi.org/10.1053/j.semperi.2013.01.006.

[21] H. Mirza, J. Garcia, G. Mckinley, L. Hubbard, W. Sensing, J. Schneider, W. Oh, R. Wadhawan, Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants, J. Perinatol. 39 (2019) 1648–1655, https://doi.org/10.1038/s41372-019-0496-5.

[22] S. Hamrick, H. Sallmon, A.T. Rose, D. Porras, E.L. Shelton, J. Reese, G. Hansmann, Patent ductus arteriosus of the preterm infant, Pediatrics 146 (2020), https://doi.org/10.1542/peds.2020-1209.

[23] A. Gudmundsdottir, S. Johansson, S. Hakansson, M. Norman, K. Kallen, A.K. Bonamy, Timing of pharmacological treatment for patent ductus arteriosus and risk of secondary surgery, death or bronchopulmonary dysplasia: a population-based cohort study of extremely preterm infants, Neonatology 107 (2015) 87–92, https://doi.org/10.1159/000367887.

[24] N.N. Finer, W.A. Carlo, M.C. Walsh, W. Rich, M.G. Gantz, A.R. Laptook, B.A. Yoder, R.G. Faix, A. Das, W.K. Poole, E.F. Donovan, N.S. Newman, N. Ambalavanan, I.R. Frantz, S. Buchter, P.J. Sanchez, K.A. Kennedy, N. Laroia, B.B. Poindexter, C.M. Cotten, K.P. Van Meurs, S. Duara, V. Narendran, B.G. Sood, T.M. O'Shea, E. F. Bell, V. Bhandari, K.L. Watterberg, R.D. Higgins, Early cpap versus surfactant in extremely preterm infants, N. Engl. J. Med. 362 (2010) 1970–1979, https://doi.org/10.1056/NEJMoa0911783.

[25] C.J. Morley, P.G. Davis, L.W. Doyle, L.P. Brion, J.M. Hascoet, J.B. Carlin, Nasal cpap or intubation at birth for very preterm infants, N. Engl. J. Med. 358 (2008) 700–708, https://doi.org/10.1056/NEJMoa072788.

[26] E.E. Foglia, E.A. Jensen, H. Kirpalani, Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants, J. Perinatol. 37 (2017) 1171–1179, https://doi.org/10.1038/jp.2017.74.

[27] C.F. Poets, L. Lorenz, Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence, Arch. Dis. Child. Fetal Neonatal Ed. 103 (2018) F285–F291, https://doi.org/10.1136/archdischild-2017-314264.

[28] J. Bates, B.J. Smith, Ventilator-induced lung injury and lung mechanics, Ann. Transl. Med. 6 (2018) 378, https://doi.org/10.21037/atm.2018.06.29.