BMC Pulmonary Medicine

RESEARCH

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Characteristics and sex differences in bronchopulmonary dysplasia-related pulmonary hypertension

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Abstract

Background Pulmonary hypertension (PH) secondary to bronchopulmonary dysplasia (BPD) is associated with increased mortality. This study aims to elucidate the risk factors for BPD-PH development and the long-term prognostic factors in pediatric BPD.

Methods We analyzed 1082 BPD patients under the age of three. Univariate and multivariate regression were performed to determine the final model. Risk stratification was performed based on the predicted risk score, and Kaplan–Meier survival curves were used to compare survival rates.

Results The in-hospital mortality rate of severe BPD was three times than non-severe BPD, and pediatric BPD-PH had twice the mortality compared to BPD without PH. The incidence of BPD was 1.7 times higher in males, but there were no sex-specific differences in BPD severity. However, female children with BPD had a higher likelihood of developing BPD-PH and lower survival rates. Females, severity of BPD, congenital diaphragmatic hernia, ventricular septal defect, patent ductus arteriosus, uric acid, aspartate aminotransferase/alanine transaminase (ALT), and albumin were independent factors of PH in BPD. Severity of BPD, PH, severe pneumonia, budesonide use, use of adrenaline or noradrenaline, ALT, and day of respiratory support were independent factors for overall survival in pediatric BPD. Two web servers were constructed based on these predictive factors for risk prediction of BPD-PH (https://sex-ph.shinyapps.io/Nomapp1/) and overall survival prediction in BPD patients (https://zds88.shinyapps.io/DynNomapp/).

Conclusion This study confirmed sex differences in BPD-PH and emphasized the role of sex in the development and prognosis of the disease. Two web servers predicted personalized PH risk and survival outcomes in BPD.

Keywords Bronchopulmonary dysplasia, Pulmonary hypertension, Sex difference, Overall survival

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Introduction

Bronchopulmonary dysplasia (BPD) is a common respiratory disease in premature infants, particularly those born very early. Its causes are complex and include incomplete alveolar development, airway inflammation, and airflow obstruction [1]. The incidence of BPD has been increasing, becoming a significant contributor to morbidity and mortality in premature infants [2, 3]. This rise may be linked to advancements in neonatal care, which have improved survival rates for high-risk preterm infants, consequently increasing BPD cases [3]. In the United States, about 10,000 to 15,000 infants are diagnosed with BPD each year [4]. Around 40% of extremely low birth weight infants (weighing less than 1000 grams) develop BPD [5], with smaller and immature infants at greater risk [3]. Early pulmonary vascular disease after preterm birth is linked to BPD, and these infants often have pulmonary vascular issues that can lead to pulmonary hypertension (PH) [6]. PH is a serious complication of BPD, associated with higher mortality and increased risk of tracheotomy [6–8].

This study aims to identify risk factors, develop personalized assessment models for infants with BPD, and investigate long-term prognosis. These models will be developed into web servers for clinicians to easily access, guiding for clinical decision-making. Additionally, the study will explore the impact of sex on BPD development and prognosis, aiming to improve treatment strategies and quality of life for affected children.

Methods

Study population

A retrospective cohort study was conducted at the Children's Hospital of Chongqing Medical University from January 2015 to December 2021. In 2018, the NICHD introduced new diagnostic criteria for BPD, defining it as persistent pulmonary parenchymal disease confirmed by imaging in preterm infants born at <32 weeks gestation, who require oxygen therapy support (for more than 3 consecutive days) at postmenstrual age (PMA) 36 weeks to maintain arterial oxygen saturation between 90% and 95%. This criterion refines the classification of BPD based on oxygen requirements and categorizes preterm infants aged >14 days with PMA <36 weeks who die from respiratory failure as having severe BPD [3]. The final diagnosis of all cases was confirmed according to the 2018 criteria and combined with relevant clinical and imaging data to ensure the reliability of the results. We excluded infants who had a neonatal intensive care unit stay of less than 3 days, who did not undergo echocardiography, or whose families were unlikely to be followed long-term. The study population consisted of infants aged ≤3 years, mainly in infancy. A total of 1082 children with BPD were included in the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The Institutional Review Committee of the Children's Hospital of Chongqing Medical University approved this study (File No.: No.8 in 2022), and the requirement for informed consent for retrospective chart review was waived [9].

Definition of outcomes

PH was defined by one or more of the following criteria: 1) elevated right ventricular pressure estimated by tricuspid regurgitation velocity (TRV) (systolic pulmonary arterial pressure estimate ⩾35 mm Hg), 2) bidirectional or right-to-left shunting through a patent ductus arteriosus, or 3) flattening or bowing of the interventricular septum in end-systole [10]. Severe PH was defined as when the right ventricular pressure exceeds 75% of systemic arterial pressure [7] or when the interventricular septum bows into the left ventricle [11]. Extremely preterm infants with severe BPD underwent BPD-PH screening at approximately 36 weeks PMA. Patent ductus arteriosus refers to the failure of the ductus arteriosus, which connects the pulmonary artery to the aorta during fetal development, to close normally after birth, resulting in abnormal blood flow [12].

Data collection

Demographic and clinical characteristics, biochemical results, treatment, and hemodynamic data (right ventricular systolic pressure (RVSP), TRV, etc.) were collected from patient registries and electronic medical records. Duration of respiratory support was calculated from admission to the neonatal intensive care unit until discharge. These data were collected during the infants' hospitalization, representing the first examination upon their initial admission. Echocardiography and laboratory tests were typically conducted within one-week post-birth. When multiple data points existed for the same variable, the data point closest to diagnosis was selected. The main outcome of this study was the incidence of PH in children with BPD and clinical factors associated with the prognosis of BPD. Overall survival was the endpoint of interest in this study and was calculated from the time of diagnosis to death from any cause or the last follow-up date in May 2023. We followed patients until they all achieved at least 3 years of age.

Statistical analysis

Fisher's exact test was used for the comparison of categorical variables between the PH and non-PH groups, while an unpaired t-test or Mann–Whitney U test (if not normal distribution) was used for continuous variables. Variables with $P<0.05$ in univariate logistic or Cox

regression were further selected using Lasso regression. Further disciplinary regression was performed by incorporating 1-s.e. independent risk factors into multivariate Logistic or Cox regression. The discrimination and calibration of the model were evaluated using the area under the receiver operating characteristic (ROC) curve (AUC) and calibration curve. The clinical utility of the model was assessed through decision curve analysis (DCA) by calculating the net benefit at different threshold probabilities. The distribution and differences of the predicted risk models between the BPD-PH and non-PH groups were analyzed and compared using violin plots. The percentage of patients in each risk level and the corresponding actual incidence of PH were presented in the form of histograms. Patients were categorized into low, medium, and high-risk groups based on the predicted risk scores using X-tiler software, and the survival rate differences were analyzed using Kaplan–Meier survival curves and log-rank tests. Multiple imputations were performed for missing values (missing rate < 20%) while missing rates ≥ 20% were not included in Lasso regression and multivariate regression. For missing data (1–15%), the multiple imputation method was applied to estimate the missing values, while variables with a high frequency of missing values were excluded from the multivariate model [13].

All statistical analyses were performed using R software version 3.4.2. Lasso logistic regression was conducted using the "glmnet" package. ROC curves were plotted using the "pROC" package. Logistic regression, model building, and calibration plots were performed using the "rms" package. DCA was performed using the "dca.R" function. Two-sided $P<0.05$ was considered statistically significant.

Results

Clinical characteristics of patients

The in-hospital mortality in this study was 3.9% (42/1082), with 33 children dying due to respiratory failure or multiple system organ failure, 2 due to toxic shock syndrome, and 7 others with unknown causes of death. The mortality during neonatal hospitalization for BPD-PH was 5.4% (26/478), which was more than twice the mortality of BPD without PH (Figure 1A.a). There was no significant difference in the in-hospital mortality between non-severe PH (21/346) and severe PH (13/132) in BPD-PH ($P=0.165$). The in-hospital mortality of severe BPD was 6.5%, which was more than three times that of non-severe BPD (Figure 1A.b). The incidence of PH in BPD was 44.2% (478/1082), and the incidence of PH increased with the severity of BPD (Figure 1A.c), with rates of 36.2% and 55.6% for non-severe BPD and severe BPD, respectively. A total of 681 male children had BPD, consisting of 277 cases (40.7%) with severe BPD and 270 cases (39.6%) with BPD-PH. Among female children, there were 401 cases of BPD, with 167 cases (41.6%) classified as severe BPD and 208 cases (51.9%) as BPD-PH. Male BPD patients are 1.7 times higher than female BPD patients, and there was no sex-specific difference in the severity of BPD ($P=0.754$), but there were sex differences in BPD-PH, with female BPD patients being more susceptible to BPD-PH (Figure 1A.d). Among patients with the same severity of PH, severe BPD patients had a longer duration of respiratory support than non-severe BPD patients ($P<0.001$); among patients with the same severity of BPD, severe PH patients had a longer duration of respiratory support than those with non-severe PH and non-PH ($P<0.001$) (Figure 1A.e). In this study, 936

(See figure on next page.)

Fig. 1 Clinical characteristics of children with BPD and Development and validation of the BPD-PH prediction model. **A** (a-e) Quantitative comparison of in-hospital mortality of BPD patients with or without PH (a), in-hospital mortality of non-severe BPD and severe BPD (b), percentage of non-severe BPD and severe BPD combining PH (c), percentage of male and female BPD combining PH (d), and days of respiratory support for BPD and PH of different severity (e). **B** The prediction model evaluates the risk of PH in in children with BPD. The total score can be easily calculated by adding the individual scores according to the proportion of each variable, and then the prediction probability of PH in children with BPD can be calculated by using the total score. **C** Male child with severe BPD, diagnosed with congenital diaphragmatic hernia, without ventricular septal defect and patent ductus arteriosus, albumin level of 33 g/L, AST to ALT ratio of 1.83, uric acid of 348.4umol/L, probability of developing PH in this patient is 0.799. **D** Calibration curves of the BPD-PH prediction model. The calibration plot illustrates the accuracy of the original prediction ("apparent") (dashed light-colored line) and the bootstrap model ("bias-corrected") (solid line) in predicting the probability of BPD patients having PH. The 45-degree line represents a perfect match between the actual probability (y-axis) and the BPD-PH prediction model (x-axis). The closer the distance between the two curves, the higher the accuracy. **E** ROC curves of the prediction model for predicting the risk of PH in children with BPD. AUC value greater than 0.7 indicates good discriminative ability, and an AUC value close to 1.0 indicates a high consistency between predicted and actual results. AUC value between 0.5 and 0.7 indicates low discriminative ability, while a value between 0.7 and 0.9 indicates moderate discriminative ability. **F** Decision curve analysis of BPD-PH plot. The y-axis represents net benefit, while the x-axis represents threshold probability. **G** The violin plot analysis compares the risk prediction probability distributions of non-PH and PH in children with BPD. The predicted risk probability in the PH group is much higher than that in the non-PH group. **H** Histogram of the percentage of actual combined PH predicted by the BPD-PH prediction model in high-risk versus low-risk patients. Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under the curve; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension. ROC, receiver operating characteristic curve

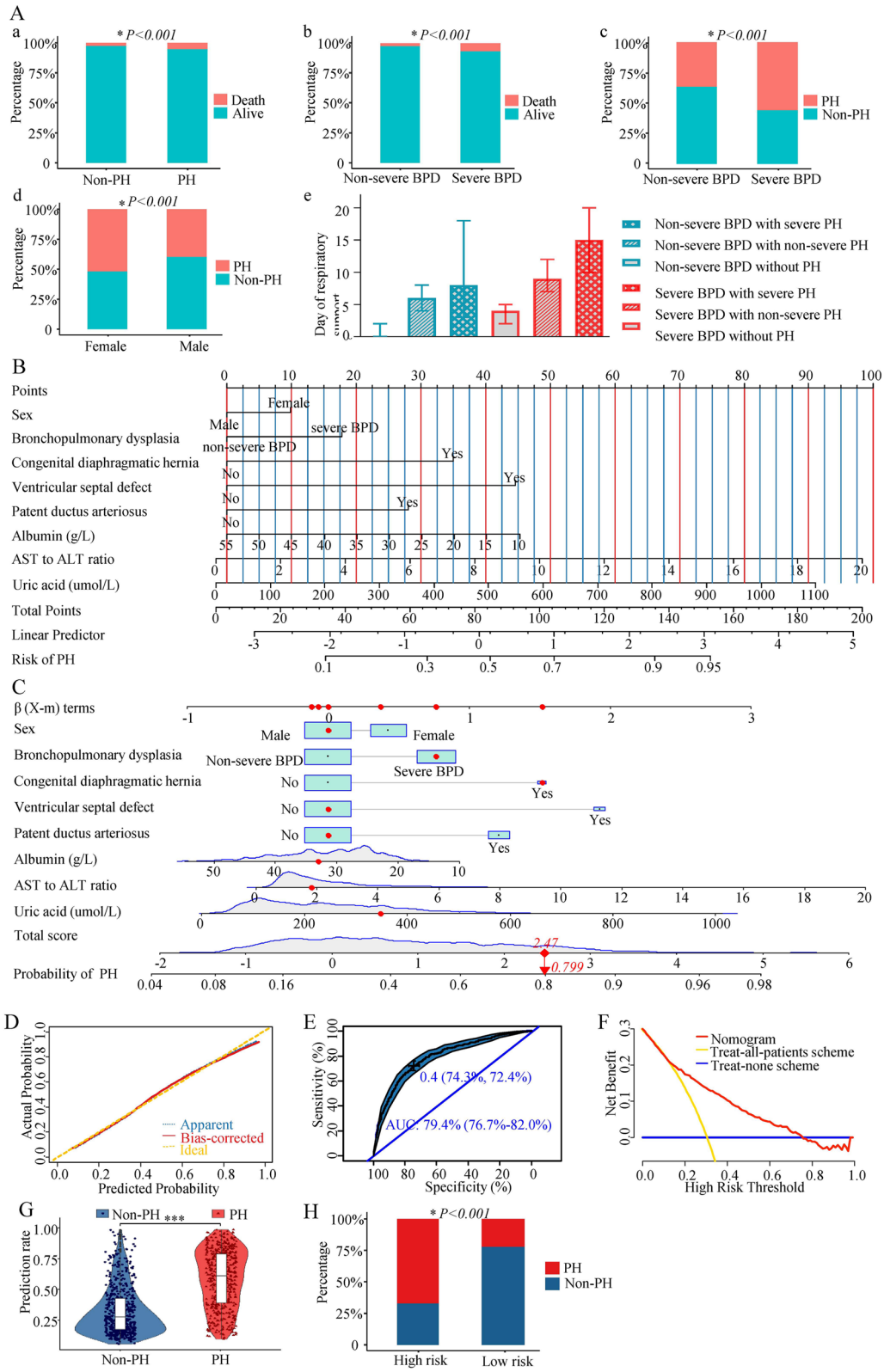

Fig. 1 (See legend on previous page.)

BPD children received budesonide, representing 86.5% of the total, including 422 BPD-PH children. A total of 365 BPD children were treated with epinephrine or norepinephrine, accounting for 33.7% of participants, of whom 205 were BPD-PH children. Additionally, 156 BPD children received theophylline, comprising 14.4% of the total, with 72 being BPD-PH children. Furthermore, 539 BPD children used short-acting beta agonists, making up 49.8% of the group, including 224 BPD-PH children. The clinical characteristics of children with BPD were shown in Table 1.

Development of BPD-PH-related model

Univariate Logistic regression analysis found that 35 predictors were related to BPD-PH (Table S1). Due to missing data exceeding 20% for TRV, RVSP, blood gas analysis parameters, and high-sensitivity cardiac troponin, they were not included in the multivariable analysis. Lasso regression was used to screen the 29 predictive factors (Figure S1A.a), and finally, 10 predictive factors were selected (Figure S1A.b). Then, a multivariable Logistic regression model was constructed for the 10 predictive factors, and it was concluded that females, BPD severity, congenital diaphragmatic hernia (CDH), ventricular septal defect, patent ductus arteriosus, albumin, ratio of aspartate aminotransferase (AST)/alanine transaminase (ALT) and uric acid were independent predictors of PH in BPD (Figure S1B). Based on these 8 predictive factors, a PH prediction model was constructed (Figure 1B), and the application of this model was shown in Figure 1C. Further analysis of the optimal cutoff values for continuous variables revealed that uric acid ≥252 umol/L, AST/ALT ratio ≥1.94, and albumin <25.8g/L were risk factors for PH in children with BPD.

Performance of the PH prediction model

The calibration curve of the model showed good consistency between predicted and observed PH incidence (Figure 1D), with an AUC of 0.794 (95% confidence interval [CI]:0.767–0.820), a sensitivity of 0.724 and a specificity of 0.743 (Figure 1E). The DCA demonstrated a positive net benefit of the model under different threshold probabilities (Figure 1F). The predicted probabilities of PH and non-PH groups by the model was 0.611 (interquartile range [IQR], 0.391–0.791) vs 0.277 (IQR, 0.178–0.430) (P<0.001) (Figure 1G). The PH probability in the high-risk group predicted by the model was 73.8% (353/478), while it was 20.7% (125/604) in the low-risk group (Figure 1H).

Basic characteristics of BPD follow-up

From the time of discharge until the follow-up time in May 2023, 96 children with BPD died, with 68 of them dying due to respiratory failure or multiple system organ failure. The survival time of the children with BPD was 50.0 months (IQR, 30.5–71.5). The survival time of BPD-PH children (43.0 months [IQR, 24.0–66.0]) was significantly lower than BPD children without PH (55.0 months [IQR, 36.0–76.0]) (P<0.001) (Figure 2A.a), but there was no significant difference in survival rates between severe and non-severe PH in BPD children (P=0.293) (Figure 2A.b). The survival rates of severe BPD children were also significantly lower than those of non-severe BPD children (P<0.001) (Figure 2A.c). Therefore, the effect of PH on the survival rate of BPD with the same severity was studied. In both non-severe BPD and severe BPD, the survival rates of PH children were significantly lower than that of children without PH (P<0.05) (Figure 2A.d). However, there was no significant difference in survival rates between non-severe BPD with PH and severe BPD without PH (P=0.775) (Figure 2A.d). The 2-year survival rates of non-severe BPD without PH, non-severe BPD with PH, severe BPD without PH, and severe BPD with PH were 92.0%, 83.7%, 81.8%, and 72.3%, respectively. The survival rates for other years were shown in Table S2. Notably, there was no sex difference in the prognosis of BPD children (P=0.058), but there was a sex difference in the prognosis of BPD-PH children, with female BPD patients having significantly lower survival rates than male patients (P=0.015) (Figure 2A.e).

Development of BPD prognosis model

Univariate Cox regression analysis found 15 predictors associated with the prognosis of BPD patients (P<0.05) (Table S3). The missing rate of TRV and RVSP was greater than 20%, so they were not included in the multivariate analysis. Lasso regression was used to screen the 15 predictive factors (Figure S1C.a), and finally, 7 predictive factors were selected (Figure S1C.b). A multivariate Cox regression model was then constructed with the 7 predictive factors, and it was determined that the severity of BPD, PH, severe pneumonia, day of respiratory support, ALT, budesonide use, and use of adrenaline or noradrenaline were significant predictors of overall survival in children with BPD (Figure S1D). Based on these 7 significant predictive factors, a BPD prognosis model was built for BPD patients (Figure 2B), and its application is shown in Figure 2C. Further analysis of the optimal cutoff values for continuous variables showed that ALT ≥55 U/L and day of respiratory support ≥22 were risk factors for the prognosis of children with BPD.

Table 1 Demographic and clinical characteristics of children with BPD

Variable	All ($n=1082$)	Non-PH ($n=604$)	PH ($n=478$)	*P* value
Sex, No. (%)				< 0.001
Male	681 (62.9)	411 (68.0)	270 (56.5)	
Female	401 (37.1)	193 (32.0)	208 (43.5)	
< 28 weeks' gestation, No. (%)	130 (12.0)	65 (10.8)	65 (13.6)	0.154
Birth weight < 1000 g, No. (%)	59 (5.5)	22 (3.6)	37 (7.7)	0.003
Day of respiratory support	4.0 [0.0, 14.0]	2.0 [0.0, 9.0]	8.0 [2.0, 22.0]	< 0.001
Atrial septal defect, No. (%)	343 (31.7)	204 (33.8)	139 (29.1)	0.099
Ventricular septal defect, No. (%)	57 (5.3)	14 (2.3)	43 (9.0)	< 0.001
Patent ductus arteriosus, No. (%)	194 (17.9)	67 (11.1)	127 (26.6)	< 0.001
Revision surgical (ASD/VSD/PDA), No. (%)	76 (7.0)	10 (1.7)	66 (13.8)	< 0.001
Tricuspid regurgitation velocity, m/s	2.2 [2.1, 2.5]	2.1 [2.0, 2.2]	2.7 [2.2, 3.1]	< 0.001
RVSP, mmHg	27.0 [24.0, 32.0]	26.0 [23.0, 28.0]	36.5 [28.8, 46.0]	< 0.001
Severe pneumonia, No. (%)	324 (29.9)	190 (31.5)	134 (28.0)	0.222
Septicemia, No. (%)	331 (30.6)	163 (27.0)	168 (35.1)	0.004
Premature infant retinopathy, No. (%)	41 (3.8)	21 (3.5)	20 (4.2)	0.545
Congenital diaphragmatic hernia, No. (%)	31 (2.9)	6 (1.0)	25 (5.2)	< 0.001
Necrotizing enterocolitis of newborn, No. (%)	48 (4.4)	29 (4.8)	19 4.0)	0.521
BPD severity, No. (%)	—	—	—	< 0.001
Non-severe BPD	638 (59.0)	407 (67.4)	231 (48.3)	—
Severe BPD	444 (41.0)	197 (32.6)	247 (51.7)	—
Budesonide use, No. (%)	936 (86.5)	514 (85.1)	422 (88.3)	0.128
Use of adrenaline or noradrenaline, No. (%)	365 (33.7)	160 (26.5)	205 (42.9)	< 0.001
Theophylline use, No. (%)	156 (14.4)	84 (13.9)	72 (15.1)	0.591
Use of short-acting beta agonists, No. (%)	539 (49.8)	315 (52.2)	224 (46.9)	0.084
Retinal photocoagulation/Vitreous injection, No. (%)	28 (2.6)	10 (1.7)	18 (3.8)	0.030
Survival status, No. (%)	—	—	—	< 0.001
Alive	675 (83.0)	382 (88.0)	293 (77.3)	—
Death	138 (17.0)	52 (12.0)	86 (22.7)	—
Survival time, month	50.0 [30.5, 71.5]	55.0 [36.0, 76.0]	43.0 [24.0, 66.0]	< 0.001
White blood cell count, * 10^9/L	9.5 [7.2, 14.1]	9.4 [7.4, 13.9]	9.6 [6.8, 14.2]	0.613
Percentage of neutrophils, %	50.0 [34.0,66.0]	47.0 [32.0,62.0]	57.0 [40.0,68.0]	< 0.001
Percentage of Lymphocyte, %	40.0 [26.0,55.0]	44.0 [28.0,57.0]	35.0 [25.0,50.0]	< 0.001
Red blood cell count, * 10^12/L	4.0 [3.4, 4.6]	3.8 [3.3, 4.5]	4.2 [3.5, 4.8]	< 0.001
Hemoglobin, g/L	122.0 [100.0, 158.0]	115.0 [97.0, 143.0]	140.0 [108.0, 168.3]	< 0.001
Platelet distribution width, %	12.5 [11.2, 14.6]	12.6 [11.2, 14.9]	12.3 [11.1, 14.2]	0.166
Procalcitonin, ng/L	0.3 [0.1, 1.1]	0.2 [0.1, 0.7]	0.4 [0.1, 1.6]	0.072
APTT, s	58.2 [42.3, 79.8]	52.7 [39.9, 73.4]	67.3 [46.4, 89.0]	< 0.001
Thrombin time, s	19.2 [17.6, 21.3]	18.6 [17.3, 20.8]	19.8 [18.0, 21.8]	< 0.001
Prothrombin time, s	13.9 [12.2, 16.3]	13.3 [11.9, 15.0]	15.1 [13.0, 17.5]	< 0.001
Fibrinogen, g/L	1.5 [1.0, 2.1]	1.6 [1.2, 2.2]	1.3 [0.9, 1.8]	< 0.001
PH value	7.4 [7.3, 7.4]	7.4 [7.3, 7.4]	7.3 [7.3, 7.4]	< 0.001
PCO_2, mmHg	44.0 [36.0, 53.0]	43.0 [36.0, 52.0]	45.0 [37.0, 54.0]	0.029
Oxygen Saturation, %	95.0 [86.0, 99.0]	94.0 [88.0, 99.0]	95.0 [85.0, 99.0]	0.697
Actual base excess, mmol/L	−1.2 [−5.2, 2.8]	−0.3 [−3.9, 3.8]	−2.6 [−6.2, 1.8]	< 0.001
Standard base excess, mmol/L	−1.4 [−4.9, 2.5]	−0.4 [−3.9, 3.1]	−2.5 [−5.9, 1.6]	< 0.001
Lactic acid, mmol/L	2.1 [1.4, 3.3]	2.0 [1.2, 3.0]	2.4 [1.4, 3.7]	0.001
Creatinine, umol/L	38.9 [23.3, 57.1]	32.1 [21.4, 50.2]	48.1 [27.8, 62.9]	< 0.001
Urea, mmol/L	3.6 [2.5, 5.0]	3.5 [2.4, 4.8]	3.7 [2.7, 5.2]	0.004
Uric acid, umol/L	222.8 [130.7, 333.4]	175.1 [110.5, 274.0]	283.0 [181.4, 381.0]	< 0.001

Table 1 (continued)

Variable	All ($n=1082$)	Non-PH ($n=604$)	PH ($n=478$)	*P* value
Alanine transaminase, U/L	23.2 [17.7, 33.9]	23.8 [17.9, 35.8]	22.4 [17.4, 30.4]	0.057
Aspartate aminotransferase, U/L	43.4 [30.8, 68.8]	37.7 [27.9, 55.4]	55.3 [36.9, 83.9]	< 0.001
AST to ALT ratio, %	1.7 [1.1, 2.9]	1.5 [1.0, 2.3]	2.3 [1.4, 3.8]	< 0.001
Glutamyl transpeptidase, U/L	114.1 [58.4, 204.0]	93.1 [50.1, 187.4]	138.6 [72.9, 227.7]	< 0.001
Alkaline phosphatase, U/L	216.8 [157.7, 310.9]	242.8 [175.6, 346.4]	195.3 [142.7, 267.5]	< 0.001
Lactic dehydrogenase, U/L	348.0 [252.0, 536.3]	308.0 [235.5, 419.0]	446.5 [283.6, 731.0]	< 0.001
hs-cTnT, ng/L	0.06 [0.03, 0.11]	0.05 [0.02, 0.09]	0.06 [0.03, 0.14]	< 0.001
Total calcium, mmol/L	2.27 [2.09, 2.44]	2.3 [2.2, 2.5]	2.2 [2.0, 2.4]	< 0.001
Total protein, g/L	30.4 [25.6, 36.6]	50.8 [44.2, 58.0]	47.0 [40.9, 54.7]	< 0.001
Albumin, g/L	30.4 [25.5, 36.5]	31.5 [26.4, 37.9]	28.7 [24.3, 34.8]	< 0.001
Bile acid, umol/L	13.0 [7.3, 25.7]	13.8 [7.5, 26.2]	12.6 [7.1, 25.2]	0.432
Total bilirubin, μmol/L	41.0 [8.6, 71.9]	27.4 [5.9, 66.4]	46.6 [15.2, 76.2]	< 0.001
Direct bilirubin, μmol/L	12.6 [5.5, 19.6]	11.3 [4.2, 18.5]	13.3 [7.6, 21.1]	0.001
Indirect bilirubin, μmol/L	18.1 [4.1, 74.3]	10.9 [3.2, 49.0]	38.9 [6.3, 104.0]	< 0.001
Glucose, mmol/L	4.7 [3.4, 5.8]	4.7 [3.6, 5.7]	4.7 [3.3, 6.0]	0.994

Performance of BPD prognosis model

The risk score plot compared the predicted results of the prognosis model with the actual survival situation, as shown in Figures 3A and 3B, showing significantly more deaths in the high-risk group compared to the low-risk group. When stratifying continuous variables based on the optimal cut-off value, a heatmap and scatter plot showed a strong correlation between predictive factors and survival outcomes. The prognosis model demonstrated good consistency between predicted survival probabilities at 1, 5, and 7 years and actual survival rates (Figure 3C). Decision curve analysis showed that there were positive net benefits when using the prognostic model for 1, 5, and 7 years (Figure 3D). The AUC for the prognosis model at 1, 5, and 7 years was consistently larger than 0.75 (Figure 3E). Based on the predicted risk scores, patients were classified into low-risk group (<67), medium-risk group (67–100), and high-risk group (≥100), and the results showed significant differences in survival rates among the three groups, with the high-risk group having significantly lower survival rates compared to the medium and low-risk groups (Figure 3F).

Implementation of the web server

To facilitate the easy and effective analysis of individualized risk for combined PH in BPD pediatric patients, as well as the overall survival prediction for BPD patients, we have developed a PH prediction model and prognosis model as online web-based software (https://sex-ph.shinyapps.io/Nomapp1/, https://zds88.shinyapps.io/DynNomapp/). Use of the PBD-PH prediction model: Left-select the patient characteristics and click the "Predict" button. Disease risk prediction and 95% CI will be shown on the right. The prognosis model: enter clinical features on the left side, check "Predicted Survival at this Follow-Up", select prediction time, click the "Predict" button, and the right side generates the "Survival plot". Click "Predicted Survival" to get the predicted survival probability and 95% CI. Click "Numeric Summary" and "Model Summary" for data tables and an overview.

Discussion

This study found that male BPD children have a 1.7 times higher incidence than females, with no sex-specific differences in BPD severity. Several clinical studies have

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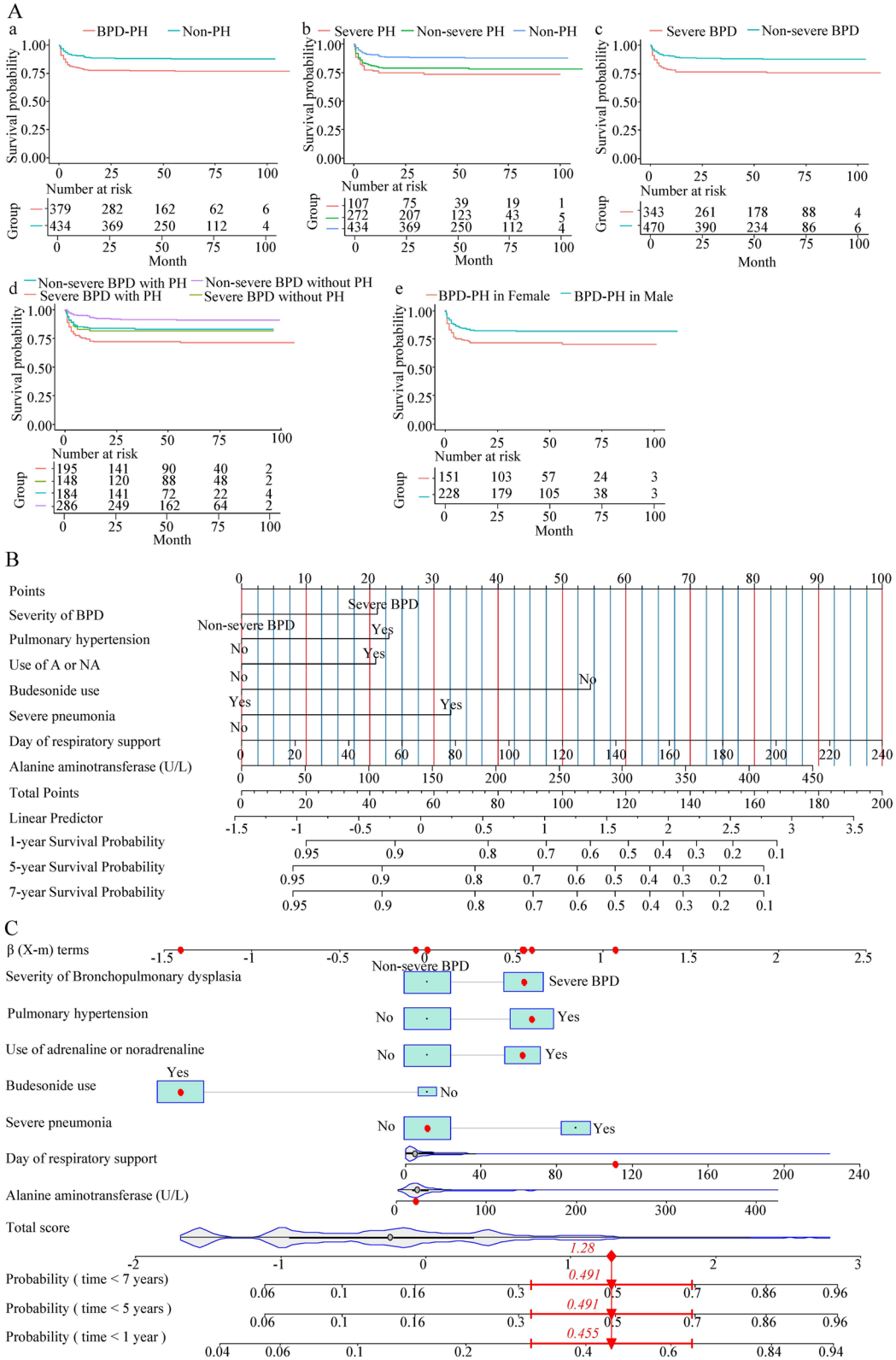
Fig. 2 Survival curve of children with BPD and Development of the BPD prognosis model. **A** (a-e) The survival curve compares the survival probability of BPD patients with or without PH (a), the survival probability of BPD children with severe PH, non-severe PH, and non-PH (b), and the survival probability of severe BPD and non-severe BPD (c), survival probability of non-severe BPD with PH, non-severe BPD without PH, severe BPD with PH, and severe BPD without PH (d), and survival probability of male and female PBD-PH children (e). **B** The prognosis model evaluates the overall survival in children with BPD. Allocate points to each variable proportionally. Add up the scores of each variable to obtain a total score, and then use the total score to calculate the overall survival predictions for 1-year, 5-year, and 7-year BPD patients. **C** Children with severe BPD who had pulmonary hypertension and had used epinephrine or norepinephrine and budesonide during hospitalization did not develop severe pneumonia, had 111 days of respiratory support, and had an ALT of 21.9 U/L. The 1-year, 5-year, and 7-year mortality predicted by this prognostic model was 0.455, 0.491, and 0.491, respectively. Abbreviations: ALT, alanine transaminase; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension



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reported sex differences in BPD, with the incidence in males being higher than that in females [14–16], and males were generally considered independent factors for BPD development [17, 18]. Previous research has demonstrated the potential therapeutic use of glucocorticoids in preventing BPD. Administering surfactant/budesonide via intratracheal injection has been shown to significantly reduce the incidence or mortality of BPD without immediate adverse effects [19]. Additionally, this study found that budesonide administration has a protective effect on the long-term prognosis of children with BPD, potentially improving their outcomes. Abnormal liver function tests were also found to be closely associated with the long-term prognosis of BPD patients. Clinicians can use ALT indicators to assess patient prognosis early on and intervene accordingly to enhance outcomes.

Additionally, this study discovered a sex difference in BPD-PH for the first time, with female BPD children having a higher risk of developing BPD-PH and lower survival rates, potentially related to physiological characteristics and genetic factors. Research showed that females were more likely than men to develop lung diseases, with higher severity, exacerbation rates, and hospitalization rates [20]. Estrogen promotes vascular proliferation and cell damage, enhancing the proliferation of pulmonary vascular smooth muscle cells [21–23]. Under normal oxygen conditions, 17β-estradiol (the main circulating estrogen) promotes the development of PH [24]. Additionally, the upregulation of Y chromosome genes in the lungs helps prevent vascular remodeling [25]. This research emphasized the need for healthcare professionals to consider sex factors when dealing with BPD-PH children.

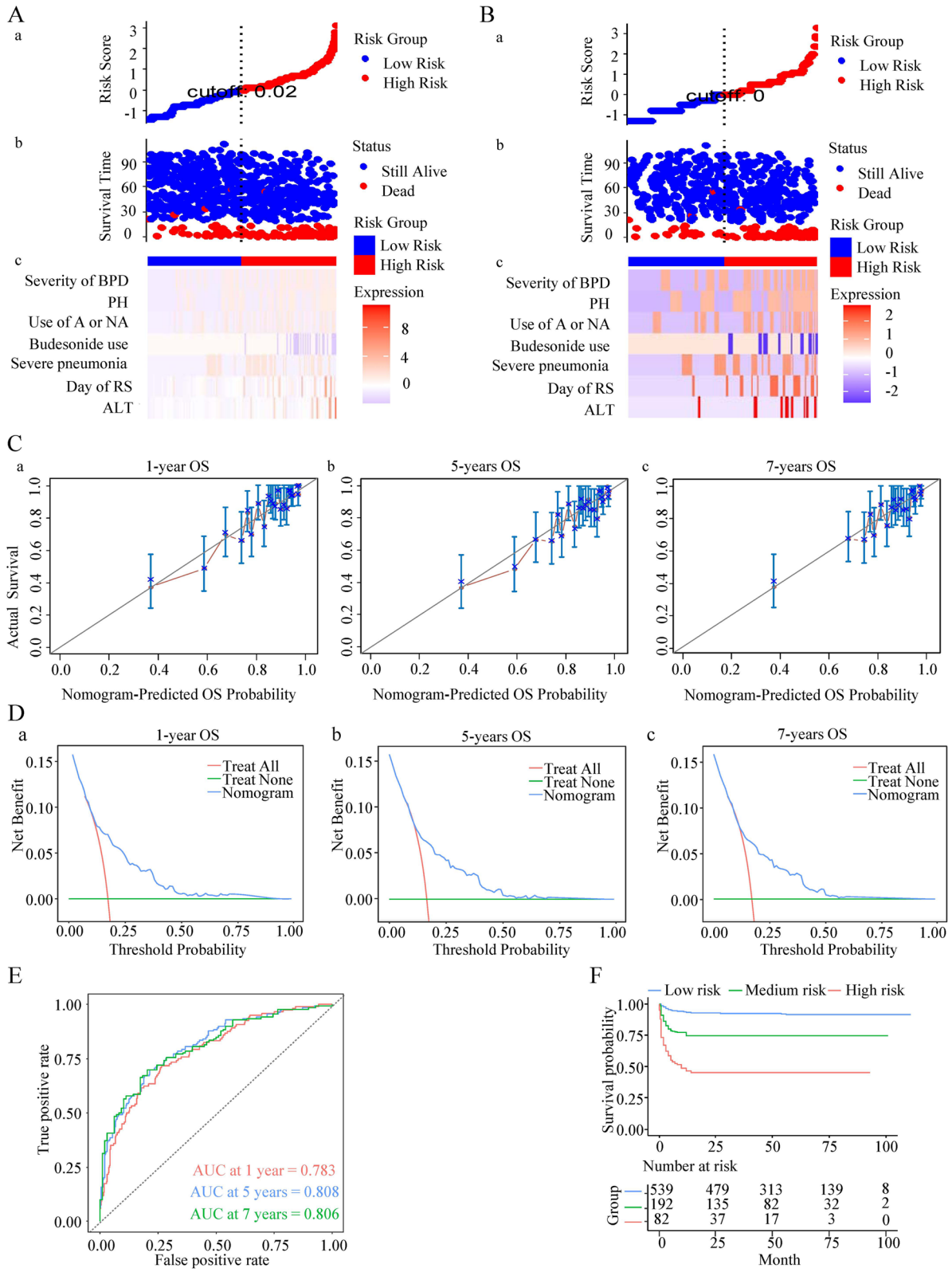
This study also revealed that the incidence of PH increases with the severity of BPD, especially in children with severe BPD where it is 1.5 times higher compared to non-severe cases. Furthermore, children with severe BPD have shorter survival rates, indicating the impact of BPD severity on survival. PH was strongly linked to higher mortality in BPD patients, with BPD-PH patients having a more than twofold higher mortality rate during hospitalization. Additionally, children with BPD-PH have shorter survival rates compared to those with BPD alone. Moreover, as BPD and PH severity increased, the duration of respiratory support also increased. These findings stressed the significance of screening and monitoring for PH in severe BPD cases to detect and implement early interventions.

Furthermore, this study identified that CDH is an important factor in the development of PH in children with BPD. CDH refers to developmental lung diseases that can increase right heart pressure and pulmonary vascular resistance, leading to PH [2, 26]. Interestingly, certain biomarkers like uric acid, AST/ALT, and albumin were associated with PH development in BPD patients. The AST/ALT ratio was considered a prognostic biomarker for PH [27]. Serum uric acid, a product of purine metabolism [28], has been confirmed as a non-invasive biomarker for PH [29, 30]. Recent studies indicated that uric acid levels can predict the severity and outcomes of pediatric PH, consistently observed from baseline throughout the disease course [31]. These biomarkers have the potential to aid in the diagnosis and treatment of PH, allowing for early interventions and personalized therapies.

We have also developed an online network software that predicts the risk of BPD-PH. Clinicians can access https://sex-ph.shinyapps.io/Nomapp1/ and provide patient information to obtain a risk prediction for BPD-PH. This model has shown higher predictive performance compared to traditional methods, enabling accurate early diagnosis and intervention for BPD-PH based on individual characteristics. Furthermore, an online web software (https://zds88.shinyapps.io/DynNomapp/) has been developed to facilitate the application of this prognostic model in clinical practice. This software can rapidly and accurately predict survival rates and classify BPD patients into corresponding risk levels based on their clinical

(See figure on next page.)

Fig. 3 Validation and risk stratification of BPD prognostic model. **A**-**B** Risk score distribution plot for children with BPD (Figure A uses continuous variables for risk assessment, while Figure B converts continuous variables into categorical variables based on the optimal intercept value for risk assessment). Patients are arranged in ascending order of risk scores from left to right (a). Survival status of each patient (b). The y-axis represents overall survival time. Color code: blue represents alive cases, and red represents deceased cases. Heatmap of expression levels for selected variables (c). **C** (a-c) Calibration curves of the 1-, 5-, and 7-year overall survival for children with BPD. The light blue line represents the ideal reference line, where the predicted probabilities match the observed survival probability. The red dots, calculated through bootstrapping (sample: 1000), represent the performance of the prognostic model. The closer the solid red line is to the light blue line, the more accurate the model's predicted survival probability. **D** (a-c) Decision curve analysis for the BPD prognostic model. The y-axis represents net profit, which is calculated by summing up the gains (true positives) and subtracting the harms (false positives). The x-axis represents threshold probability. **E** ROC curve of the 1-, 5-, and 7-year survival prediction for BPD prognostic model. **F** Kaplan–Meier overall survival curves for the low-risk, medium-risk and high-risk BPD patients stratified by the BPD prognostic model. Abbreviations: A, adrenaline; ALT, alanine transaminase; AUC, area under the curve; BPD, bronchopulmonary dysplasia; NA, noradrenaline; OS, overall survival; PH, pulmonary hypertension; RS, respiratory support; ROC, receiver operating characteristic curve



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information. It was a valuable tool for physicians to better evaluate the prognosis of BPD patients and take appropriate treatment measures.

Major limitations of our study included relying on data from a single institution and the necessity for validation from other centers. Also, the retrospective study design limited the ability to infer causal relationships and may introduce selection or information bias. Echocardiography has limitations in diagnosing PH, while cardiac catheterization is more accurate but carries risk. The risk of adverse events associated with cardiac catheterization in pediatric PH ranges from 1.4% to 3.5%, with higher risk in infants and children under 2 years old [32, 33]. Prospective studies are needed for further confirmation. In addition, our prognostic model still lacked some specific biomarkers to better predict the prognosis of BPD. For example, missing factors included weight gain, level of ventilation support, gestational age at birth, total parenteral nutrition dependency, inhaled nitric oxide support, sildenafil or other anti-PH medication, and trach dependency.

In conclusion, this study revealed the existence of sex differences in BPD-PH and highlighted the importance of sex in the development and prognosis of this disease. Further research can delve into its mechanisms and develop individualized treatment strategies targeting sex differences. Additionally, this study has constructed two web servers for predicting the individualized risk of developing PH in children with BPD and predicting overall survival.

Abbreviations

ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
CDH	Congenital diaphragmatic hernia
CI	Confidence interval
DCA	Decision curve analysis
IQR	Interquartile range
PH	Pulmonary hypertension
PMA	Postmenstrual age
ROC	Receiver operating characteristic curve
RVSP	Right ventricular systolic pressure
TRV	Tricuspid regurgitation velocity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03585-1.

Supplementary Material 1.

Acknowledgements

None.

Authors' contributions

Dr Dansha Zhou, Dr Ting Wang, and Prof Yuqin Chen designed the study, collected specimens, analyzed and interpreted the data, wrote the manuscript, performed data analysis. Dr Yulin Zheng, Dr Yingzhen Zhou, Dr Mingxiang Zhang, Dr Aofeng Liu, Dr Biao Hu, Dr Shuang Fu, Dr Ruixian Wu, Dr Wei Chen, Dr Xiaoli Jiang, Dr Zehui Ye, Dr Yuan Shi, and Prof Zhou Fu contributed to the clinical diagnosis of BPD and interpretation of data. Prof Jian Wang contributed to the study design, provided financial support, performed data analysis and interpretation, wrote the manuscript, and provided final approval. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This work was supported in part by the grants from the National Natural Science Foundation of China (82170069, 82120108001, 82241012, 82370063), National Key R&D Program of China (2022YFE0131500), R&D Program of Guangzhou National Laboratory (GZNL2023A02013), Local Innovative and Research Teams Project of Guangdong Pearl River Talents Program (2017BT01S155), Guangdong Department of Science and Technology (2024A1515011208), Basic Science and Application of Guangzhou Science and Technology Plan (202201010069), Chongqing Postdoctoral International Exchange Training Program (2021JLPY001), Guangzhou Basic Research Program Municipal School (Hospital) Joint Funded Foundation and Application Basic Research Project (202201020384), Independent Project of State Key Laboratory of Respiratory Disease (SKLRD-Z-202101), open Research Funds from The Sixth Affiliated Hospital of Guangzhou Medical University (Qingyuan People's Hospital) (202201–101) and Nanshan Talent Project of the First Affiliated Hospital of Guangzhou Medical University and National Clinical Medical Research Center (NCRC-2022-GP-08).

Data availability

All data included in this study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Committee of the Children's Hospital of Chongqing Medical University, with the ethics committee approval number (2022) Ethics Review (Research) No. (8). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The requirement for informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 19 September 2024 Accepted: 6 March 2025
Published online: 01 April 2025

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