A prediction nomogram for neonatal acute respiratory distress syndrome in late-preterm infants and full-term infants: A retrospective study

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Summary

Background Neonatal acute respiratory distress syndrome (ARDS) is a critical clinical disease with high disability and mortality rates. Early identification and treatment of neonatal ARDS is critical. This study aimed to build a perinatal prediction nomogram for early prediction of neonatal ARDS.

Methods A prediction model was built including 243 late-preterm and full-term infants from Daping Hospital in Chongqing, China, hospitalised between Jan 1, 2018 and Dec 31, 2019. 80 patients from the Children's Hospital in Chongqing, China, hospitalised between Jan 1, 2018 and June 30, 2018 were considered for external validation. Multivariate logistic regression was performed to identify independent predictors and establish a nomogram to predict the occurrence of neonatal ARDS. Both discrimination and calibration were assessed by bootstrapping with 1000 resamples.

Findings Multivariate logistic regression demonstrated that mother's education level (odds ratio [OR] 0·478, 95% confidence interval [CI] 0·324–0·704), premature rupture of membrane (OR 0·296, 95% CI 0·133–0·655), infectious disease within 7 days before delivery (OR 0·275, 95% CI 0·083–0·909), hospital level (OR 2·479, 95% CI 1·260–4·877), and Apgar 5-min score (OR 0·717, 95% CI 0·563–0·913) were independent predictors for neonatal ARDS in late-preterm and full-term infants, who experienced dyspnoea within 24 h after birth and required mechanical ventilation. The area under the curve and concordance index of the nomogram constructed from the above five factors were 0·760 and 0·757, respectively. The Hosmer–Lemeshow test showed that the model was a good fit (P = 0.320). The calibration curve of the nomogram was close to the ideal diagonal line. Furthermore, the decision curve analysis demonstrated significantly better net benefit in the model. The external validation proved the reliability of the prediction nomogram.

Interpretation A nomogram based on perinatal factors was developed to predict the occurrence of neonatal ARDS in late-preterm and full-term infants who experienced dyspnoea within 24 h after birth and required mechanical ventilation. It provided clinicians with an accurate and effective tool for the early prediction and timely management of neonatal ARDS.

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Keywords: Neonatal acute respiratory distress syndrome; Late-preterm infants; Full-term infants; Prediction nomogram

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Introduction

De Luca et al.[1] first proposed the Montreux definition of neonatal acute respiratory distress syndrome (ARDS)

Research in context

Evidence before this study

We searched PubMed and Google Scholar without any language restrictions for articles published between Jan 1, 2000, and May 31, 2021, using the search terms "acute respiratory distress syndrome (ARDS)" AND "neonates" AND "prediction model" AND "perinatal factors". De Luca et al. first proposed the Montreux definition of neonatal ARDS in 2017, and several reports on neonatal ARDS published since have mainly focused on clinical manifestations, treatment strategies, and prognosis. To the best of our knowledge, no risk prediction model of perinatal factors has been established to predict the occurrence of neonatal ARDS.

Added value of this study

We found that mother's education level, premature rupture of membrane, infectious disease within 7 days before delivery, hospital level, and Apgar 5-min score were independent predictors for neonatal ARDS in late-preterm infants and full-term infants who experienced dyspnea within 24 h after birth and required mechanical ventilation. We built a visual and personalised nomogram model based on these perinatal factors for the early prediction and treatment of ARDS, and external validation confirmed the accuracy and conformity of the model, and better net benefit.

Implications of all the available evidence

The model provides clinicians with a simple and intuitive tool for practical prediction which may significantly reduce the mortality of neonatal ARDS. These findings may also lay the foundation for future research on the pathogenesis of neonatal ARDS.

based on ARDS in adults and older children in 2017, considering that the aetiology of neonatal ARDS may differ from that of adults and older children, existing clinical tools and monitoring techniques in adults and older children are unsuitable for neonates. Although substantial progress has been made in neonatal ARDS in recent years, it remains a life-threatening syndrome, with relatively high rates of disability or mortality.[2] A multicentre study in China reported that the mortality rate of severe neonatal ARDS with a gestational age (GA) ≥36 weeks was 25·2%.[3] Compared with neonatal respiratory distress syndrome (RDS) incurred by primary pulmonary surfactant deficiency, neonatal ARDS may be more likely to affect late-preterm and full-term infants.[3,4] However, the aetiology and pathogenesis of neonatal ARDS remain unclear.

The Montreux definition indicates that perinatal factors may be an important cause of neonatal ARDS.[1] Meanwhile, numerous studies had shown that perinatal factors had a great impact on the foetus or/and newborn. Adverse conditions could lead to abortion, stillbirth, foetal distress, neonatal respiratory distress, neonatal sepsis, and even death after birth.[5–7] Therefore, as a disease with rapid progress and high mortality, it is critical to predict the possibility of neonatal ARDS using perinatal factors prior to delivery. However, thus far, there remain few reports on the correlation between perinatal factors and neonatal ARDS, and no risk prediction model of perinatal factors has been established to predict the occurrence of neonatal ARDS. As a simple statistical visual tool, the nomogram is widely used to predict the occurrence, development, prognosis, and survival of diseases in recent years.[8–11]

This retrospective study sought to establish a prediction nomogram. To this end, the model incorporated a series of perinatal factors for the early prediction and timely management of neonatal ARDS. Since the model is mainly focused on the early prediction of neonatal ARDS caused by maternal risk factors, infants with ARDS due to maternal factors usually require different degrees of respiratory support within 24 h after birth, and the possibility of respiratory distress due to ARDS in late preterm and full-term infants is greater than that in early preterm infants. Therefore, in the initial research design, the late preterm and full-term infants who required ventilation within the first 24 h of life were selected as objects for the early prediction of ARDS, not only improving the accuracy of prediction, but also conferring great clinical value.

Methods

Study design and population

This study was designed as a retrospective investigation of the data from enrolled neonates managed at Daping Hospital and Children's Hospital. The study protocol was approved by the Ethics Committees of Daping Hospital, Army Medical University (2016 NO·71) and Children's Hospital, Chongqing Medical University (2018 NO·129) with a waiver for informed consent.

In the training cohort, the retrospective study consisted of 243 neonates who were hospitalised at Daping Hospital in Chongqing, China, between Jan 1, 2018 and Dec 31, 2019. In the validation cohort, 80 neonates were hospitalised at Children's Hospital in Chongqing, China, from Jan 1, 2018 to June 30, 2018. Inclusive criteria were as follows: (a). 34 weeks ≤ GA < 42 weeks, and (b). experienced dyspnoea within 24 h after birth and required mechanical ventilation. Exclusion criteria were as follows: (a). GA < 34 weeks or GA ≥ 42 weeks, (b). RDS, transient tachypnoea of the neonate (TTN), or congenital anomalies as a primary current acute respiratory condition, (c). hereditary endocrine and metabolic diseases, or (d). incomplete records. All the patients in this study were of Han ethnicity.

Data collection

The collected data from enrolled neonates included the general conditions of the neonate (GA, birth weight, gender, Apgar score at 5 min, amniotic fluid contamination and mode of delivery), general conditions of the mother (maternal age, mother's education level, smoking/drug, regular antenatal care, hospital level of antenatal care, pre-existing disease before pregnancy), risk factors associated with maternal infection 7 days before delivery (premature rupture of membrane [PROM], chorioamnionitis [CA], infectious disease within 7 days before delivery), risk factors associated with hypoxia in late pregnancy (foetal distress, umbilical cord abnormality and placenta abnormality) and pregnancy complications (gestational diabetes mellitus [GDM], intrahepatic cholestasis of pregnancy[ICP], hypertensive disorders of pregnancy [HDP] and other complications).

Definitions

The diagnosis of neonatal ARDS was reached according to the Montreux definition (Table S1).[1] The identification of ARDS and RDS was carried out as represented in Table S2.[12] Education was measured according to the length of formal education completed, and categorized as ≤9 years (low), between 10 and 12 years (intermediate), and ≥13 years (high). The hospital level of antenatal care corresponded to level III and level II or below. Infectious disease within 7 days before delivery was assessed, as bacterial, viral or other pathogen infections in various systems that occurred in pregnant women within 7 days before delivery. Umbilical cord abnormality was assessed as being too long or too short, or having signs of oedema, torsion, or a knot, among others. Placenta abnormalities included placental abruption, placenta previa, or an abnormal placenta shape, size and weight, among others.

Development and assessment of the nomogram

A multivariate logistic regression was used to construct a nomogram model to predict the occurrence of neonatal ARDS. Independent predictors ($P < 0{\cdot}05$) were assessed by a multivariate logistic regression and then recruited to develop the nomogram using the data for predicting the occurrence of neonatal ARDS. Predictor lines were drawn upward to confirm the points received from the nomogram. The sum of these points was located on the "Total Points" axis; subsequently, a line was drawn downward to project on the bottom scales, which determined the possibility of neonatal ARDS. Thereafter, the visual prediction model was externally validated. The Hosmer–Lemeshow test and coefficient of determination (R^2) were used to assess the goodness of fit of the model. The receiver operating characteristic (ROC) curve, area under the ROC curve (AUC), concordance index (C-index), and calibration curve were used to evaluate the predictive accuracy and conformity of the model. The decision curve analysis (DCA) reflected the net benefit of the model for patients. Both discrimination and calibration were assessed by bootstrapping with 1000 resamples.

Statistical analysis

The sample size was estimated using PASS version 11·0·7. All available samples were utilized in this study. All statistical analyses were performed using R version 4·0·3 software with rms, pROC, ggplot2 and dca packages. For parameters with continuous data, the normal distribution was expressed as mean ± standard deviation, and the skewed distribution was expressed as median (M) and quartile range (P25–P75). Count data were expressed as rate (%). All statistical tests were two-sided and P value <0·05 was considered significant.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Results

General characteristics

In the training cohort, the clinical information a total of 331 patients was obtained from Daping Hospital, Army Medical University; 88 did not meet the inclusion criteria, 21 of 88 had incomplete records, which meant the absence of some items in the collected data, including maternal age, mother's education level, pre-existing disease before pregnancy, CA and placenta abnormality. Apart from above five variables with incomplete records, the remaining variables between eligible cases and incomplete cases showed no significant differences (Table S3). Finally, 243 patients were enrolled in this study (Figure 1). The minimum sample size was 148 according to calculations carried out in PASS version 11·0·7 ($\alpha = 0{\cdot}05$, power[1-β] = 0·9, and R^2 of the prediction model was 0·15). In our study, the data from 243 patients from Daping Hospital were used to construct the nomogram, which was able to meet the sample size requirement (power = 0·9976). The rates of mothers with low, intermediate and high educational level were 22.6%, 20.2% and 57.2%, respectively. In total, 39·5% of the mothers received antenatal care in level II or below hospitals, 25·5% had PROM, and 8·6% suffered from infectious disease within 7 days before delivery. The median Apgar 5-min score was 10 (Table 1).

In the validation cohort, 80 patients from Children's Hospital, Chongqing Medical University were used for external validation purposes (A flow chart of patient selection was shown in Figure S1). The rates of mothers

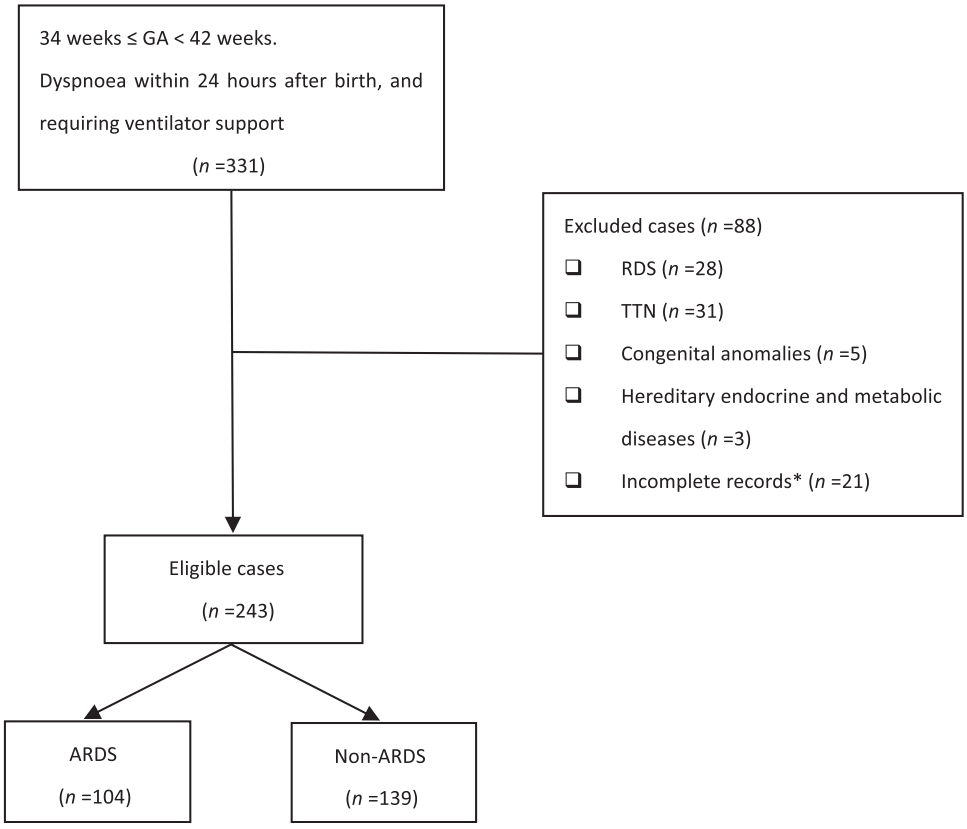

Figure 1. Flow chart for patient selection. GA = gestational age; RDS = respiratory distress syndrome; TTN = transient tachypnoea of the neonate; ARDS = acute respiratory distress syndrome. *Maternal age (n = 3), mother's education level (n = 6), chorioamnionitis (n = 5), placenta abnormality (n = 3), mother's education level and chorioamnionitis (n = 2), maternal age and pre-existing disease before pregnancy (n = 2).

with low, intermediate and high educational level were 26·3%, 23·8% and 50·0%, respectively. In total, 37·5% of the mothers received antenatal care in level II or below hospitals, 20·0% had PROM, and 15·0 % suffered from infectious disease within 7 days before delivery. The median Apgar 5-min score was 10 (Table 1).

According to the Montreux definition of neonatal ARDS, 104 patients (104/243, 42·8%) who were hospitalised at Daping Hospital were included in the ARDS group, and 139 patients (139/243, 57·2%) were included in the non-ARDS group. The diagnoses of non-ARDS patients reflected neonatal pneumonia that did not meet the diagnostic criteria for neonatal ARDS. There were no significant differences in GA, birth weight or gender between the two groups, twenty-two perinatal factors were listed (Table 2).

Screening for predictive factors

A multivariate logistic regression analysis showed that five perinatal factors were independent predictors of neonatal ARDS, per the following results: mother's education level (P = 0·000, odds ratio[OR] 0·478, 95% confidence interval [CI] 0·324–0·704), PROM (P = 0·003, OR 0·296, 95% CI 0·133–0·655), infectious disease within 7 days before delivery (P = 0·034, OR 0·275, 95% CI 0·083–0·909), hospital level (P = 0·009, OR 2·479, 95% CI 1·260–4·877), and Apgar 5-min score (P = 0·007, OR 0·717, 95% CI 0·563 –0·913) (Table 2).

Risk prediction nomogram development

The logistic regression model was constructed based on the above five factors (Table S4), after which these five perinatal factors from the logistic regression model were integrated to the nomogram (R^2 = 0·268, C-index = 0·757) (Figure 2). For each patient, higher total points indicated a higher risk of neonatal ARDS. For example, if a mother has 11 years of education (10–12 years), PROM, an infectious disease within 7 days before delivery, and antenatal care in a tertiary hospital, and if the Apgar 5-min score of her infant is 8, then the corresponding score of her infant will be approximately 33, 22, 44·2, 0, 24·4, respectively. The total score is approximately 123·6, indicating an estimated ARDS of

Variables		Training cohort(n = 243) M (P25, P75)/N (%)	Validation cohort(n = 80) M (P25, P75)/N (%)	P-value
GA (weeks)		36·9 (35·3, 39·4)	37·9 (36·1, 39·6)	0·232
Birth weight (kilograms)		2·9 (2·5, 3·4)	3·2 (2·6, 3·4)	0·125
Gender	Male	137 (56·4)	53 (66·3)	0·120
	Female	106 (43·6)	27 (33·8)	
Apgar 5-min		10 (9, 10)	10 (9, 10)	0·346
Amniotic fluid contamination	+	69 (28·4)	19 (23·8)	0·418
	−	174 (71·6)	61 (76·3)	
Mode of delivery	Caesarean delivery	171 (70·4)	57 (71·3)	0·881
	vaginal delivery	72 (29·6)	23 (28·8)	
Maternal age (years)	20-35	194 (79·8)	65 (81·3)	0·783
	<20 or ≥35	49 (20·2)	15 (18·8)	
Mother's education level (years)	≤9	55 (22·6)	21 (26·3)	0·531
	10-12	49 (20·2)	19 (23·8)	
	≥13	139 (57·2)	40 (50·0)	
Smoking/Drug	+	3 (1·2)	2 (2·5)	0·785
	−	240 (98·8)	78 (97·5)	
Regular antenatal care	+	240 (98·8)	74 (92·5)	0·010
	−	3 (1·2)	6 (7·5)	
Hospital level	level III	147 (60·5)	50 (62·5)	0·750
	level II or below	96 (39·5)	30 (37·5)	
Pre-existing disease before pregnancy	+	32 (13·2)	11 (13·8)	0·894
	−	211 (86·8)	69 (86·3)	
PROM	+	62 (25·5)	16 (20·0)	0·318
	−	181 (74·5)	64 (80·0)	
CA	+	17 (7·0)	1 (1·3)	0·096
	−	226 (93·0)	79 (98·8)	
Infectious disease within 7 days before delivery	+	21 (8·6)	12 (15·0)	0·103
	−	222 (91·4)	68 (85·0)	
Fetal distress	+	41 (16·9)	13 (16·3)	0·897
	−	202 (83·1)	67 (83·8)	
Umbilical cord abnormality	+	67 (27·6)	15 (18·8)	0·116
	−	176 (72·4)	65 (81·3)	
Placenta abnormality	+	35 (14·4)	15 (18·8)	0·351
	−	208 (85·6)	65 (81·3)	
GDM	+	72 (29·6)	12 (15·0)	0·010
	−	171 (70·4)	68 (85·0)	
ICP	+	21 (8·6)	5 (6·3)	0·495
	−	222 (91·4)	75 (93·8)	
HDP	+	27 (11·1)	5 (6·3)	0·207
	−	216 (88·9)	75 (93·8)	
Other complications	+	61 (25·1)	11 (13·8)	0·034
	−	182 (74·9)	69 (86·3)	

***Table 1*: Baseline characteristics of all patients in the training cohort and validation cohort.**
+= yes; −= no; GA = gestational age; Hospital level = The level of hospital where mothers went for antenatal care; PROM = premature rupture of membrane; CA = chorioamnionitis; GDM = gestational diabetes mellitus; ICP = intrahepatic cholestasis of pregnancy; HDP = hypertensive disorders of pregnancy.

88% for this case. In addition, The Hosmer–Lemeshow test demonstrated that the model was a good fit (P = 0.320).

Predictive accuracy and net benefit of the nomogram

In the training cohort, the AUC was 0·760 (Figure 3A), and the calibration curve was close to the ideal diagonal line (Figure 4A). Furthermore, the DCA showed significantly better net benefit in the predictive model (Figure 5A).

In addition, 80 patients from Children's Hospital were used for the external validation to test the nomogram. The AUC was 0·854 (Figure 3B), reflecting a good accuracy of the nomogram. Meanwhile, the model had good consistency, and the calibration curve of the

Variables		ARDS(n = 104) M (P25, P75)/N (%)	Non-ARDS(n = 139) M (P25, P75)/N (%)	P-value	OR	OR 95% CI	
GA (weeks)		37·9 (35·4, 39·4)	36·4 (35·1, 39·0)	0·069	2·131	0·942	4·819
Birth weight(kilograms)		3·1 (2·6, 3·5)	2·8 (2·3, 3·4)	0·190	1·792	0·748	4·291
Gender	Male	64 (61·5)	73 (52·5)	0·287	0·700	0·363	1·350
	Female	40 (38·5)	66 (47·5)				
Apgar 5-min		10 (8, 10)	10 (9, 10)	0·007	0·717	0·563	0·913
Amniotic fluid contamination	+	37 (35·6)	32 (23·0)	0·944	1·030	0·449	2·365
	−	67 (64·4)	107 (77·0)				
Mode of delivery	Caesarean delivery	72 (69·2)	99 (71·2)	0·586	1·235	0·577	2·646
	vaginal delivery	32 (30·8)	40 (28·8)				
Maternal age(years)	20-35	82 (78·8)	112 (80·6)	0·723	0·855	0·360	2·031
	<20 or ≥35	22 (21·1)	27 (19·4)				
Mother's education level(years)	≤9	34 (32·7)	21 (15·1)	0·000	0·478	0·324	0·704
	10-12	28 (26·9)	21 (15·1)				
	≥13	42 (40·4)	97 (69·8)				
Smoking/Drug	+	2 (1·9)	1 (0·7)	0·676	0·507	0·021	12·201
	−	102 (98 ·1)	138 (99·3)				
Regular antenatal care	+	101 (98·1)	138 (99·3)	0·660	1·758	0·142	21·745
	−	2 (1·9)	1 (0·7)				
Hospital level	level III	49 (47·1)	98 (70·5)	0·009	2·479	1·260	4·877
	level II or below	55 (52·9)	44 (31·7)				
Pre-existing disease before pregnancy	+	14 (13·5)	18 (12·9)	0·173	0·520	0·203	1·331
	−	90 (86·5)	121 (87·1)				
PROM	+	32 (30·8)	30 (21·6)	0·003	0·296	0·133	0·655
	−	72 (69·2)	109 (78·4)				
CA	+	10 (9·6)	7 (5·0)	0·526	0·663	0·187	2·359
	−	94 (90·4)	132 (95·0)				
Infectious disease within 7 days before delivery	+	15 (14·4)	6 (4·3)	0·034	0·275	0·083	0·909
	−	89 (85·6)	133 (95·7)				
Fetal distress	+	26 (25·0)	15 (10·8)	0·055	0·399	0·156	1·018
	−	78 (75·0)	124 (89·2)				
Umbilical cord abnormality	+	31 (29·8)	36 (25·9)	0·670	0·862	0·436	1·706
	−	73 (70·2)	103 (74·1)				
Placenta abnormality	+	20 (19·2)	15 (10·8)	0·103	0·465	0·185	1·168
	−	84 (80·8)	124 (89·2)				
GDM	+	30 (28·9)	42 (30·2)	0·524	0·795	0·393	1·609
	−	74 (71·1)	97 (69·8)				
ICP	+	9 (8·7)	12 (8·6)	0·430	0·625	0·194	2·008
	−	95 (91·3)	127 (91·4)				
HDP	+	9 (8·7)	18 (12·9)	0·966	1·024	0·344	3·047
	−	95 (91·3)	121(87·1)				
Other complications	+	24 (23·1)	37 (26·6)	0·480	0·761	0·358	1·621
	−	80 (76·9)	102 (73·4)				

***Table 2*: General characteristics of the patients and multivariate logistic regression analyses for screening predictors.**
+= yes; −= no; GA = gestational age; Hospital level = The level of hospital where the mother went for antenatal care; PROM = premature rupture of membrane; CA = chorioamnionitis; GDM = gestational diabetes mellitus; ICP = intrahepatic cholestasis of pregnancy; HDP = hypertensive disorders of pregnancy; OR = odds ratio; CI = confidence interval; L = lower limit; U = upper limit.

validation cohort was also close to the ideal diagonal line (Figure 4B). Moreover, the DCA showed significant net benefit of the predictive model, as well as that in the validation cohort (Figure 5B) (Net benefits for different threshold probabilities were showed in Table S5). These data demonstrated that our nomogram had a significant potential for clinical decision-making.

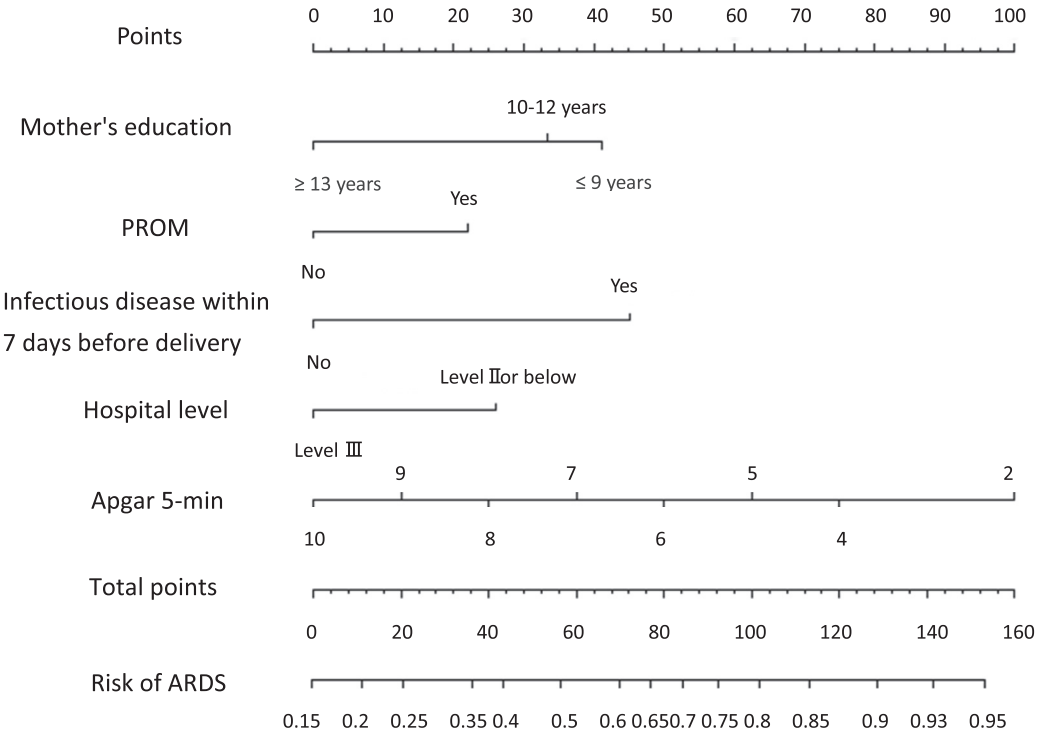

Figure 2. Nomogram for the perinatal prediction of neonatal ARDS. ARDS = acute respiratory distress syndrome.

Discussion

Our study is the first to develop a model for predicting the occurrence of neonatal ARDS using perinatal factors, although several reports about neonatal ARDS have mainly focused on clinical manifestations, treatment strategies and prognosis.[3,4,13,14] This study revealed that mother's education level, PROM, infectious disease within 7 days before delivery, hospital level and Apgar 5-min score were predictors of neonatal ARDS in late-preterm and full-term infants who experienced dyspnoea within 24 h after birth and required mechanical ventilation.

As we know, mother's education was strongly associated with certain adverse outcomes in newborns (i.e., preterm birth, low Apgar score, respiratory distress, cerebral distress, birth defects and small for gestational age).[15,16] Newborns with less educated mothers were more likely to experience neonatal complications.[17] Cantarutti et al.[16] reported that mothers with lower levels of education were at a higher risk of having infants with several neonatal adverse outcomes; compared with mothers with higher levels of education, those with lower levels of education had 19%, 22%, 18%, and 16% increased risks of preterm birth, low birth weight, small for gestational age and respiratory distress, respectively. A study in rural northwestern China found that an infection during pregnancy was associated with increased risk of birth defects and low birth weight, particularly in younger, less educated and poor pregnant women.[6] Our study also indicated that mother's education level was an independent predictor of neonatal ARDS and was included in the predictive model. The lower the mother's educational level, the higher the points in the nomogram model, and the higher the probability of neonatal ARDS. These results are not difficult to understand, mothers with low education level may not pay enough attention to pregnancy and fail to recognise dangerous signals during pregnancy. Therefore, health education programs for pregnant women with low education levels is very important, especially on pre-pregnancy and pregnancy health care, to prevent the occurrence of adverse outcomes of newborns.

CA is generally considered reflective of intrauterine infection/intra-amniotic inflammation.[18] CA with GA ≥ 34 weeks was associated with a nearly 3·5-fold increased odds of adverse neonatal outcome; the incidence of neonatal respiratory distress, neonatal mechanical ventilation, and NICU admission increased significantly.[19] Histomorphological findings from foetal and neonatal lungs exposed to intrauterine infection/inflammation demonstrated signs of inflammatory infiltration, less alveolar vesicular structure and alveolar numbers, and thickened alveolar septa; meanwhile, the expression levels of interleukin-1β (IL-1β), IL-6, tumour necrosis factor alpha (TNF-α) were significantly up-regulated.[20] These proinflammatory cytokines played important

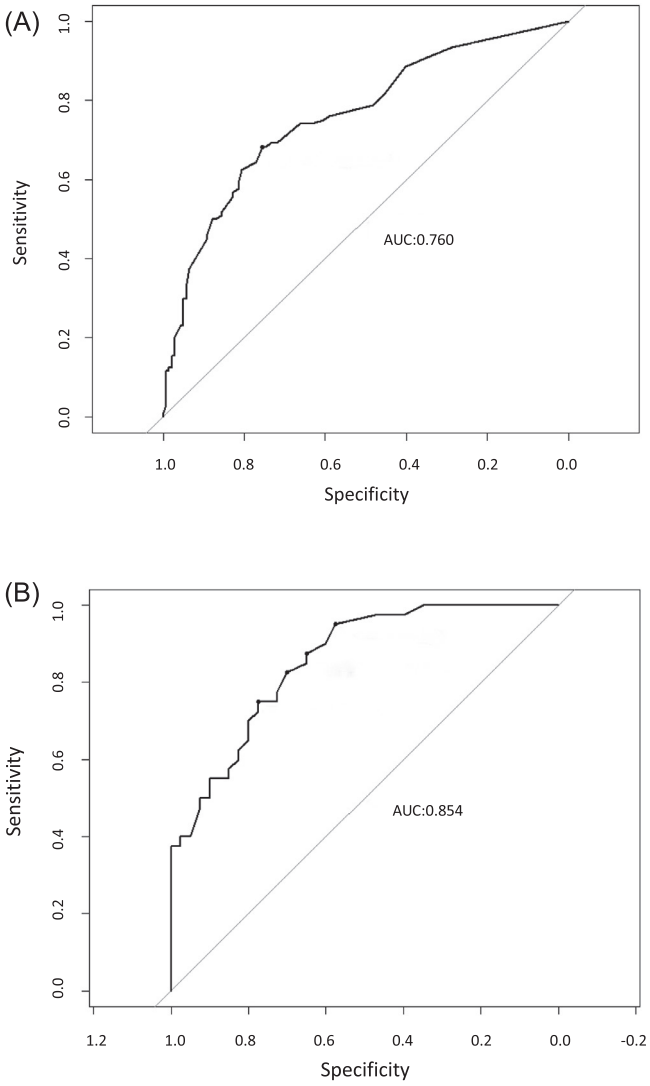

Figure 3. ROC curves. (A) Training cohort. (B) Validation cohort. ROC=receiver operating characteristic; AUC=area under the ROC curve.

roles in the pathogenesis of ARDS.[21–23] However, most intrauterine infections are subclinical, and hard to be detected without pathological or histological findings.[24] In recent years, "sterile" intra-amniotic inflammation (amniotic fluid in the absence of demonstrable microorganisms detected with culture or molecular methods), including acute histological chorioamnionitis and funisitis, has been gradually recognised.[18,25] In this study, only 7·0% (17/243) patients in the training cohort had CA, without significant difference between the ARDS and non-ARDS groups, although the rate of CA was slightly higher in the ARDS group (9·6% vs 5·0%), which could be related to the inability of some hospitals to carry out pathological examinations and the insufficient attention of medical staff, particularly in primary hospitals. However, we found that PROM was an independent predictor of neonatal ARDS and was included in the predictive model. This result reflects that the early prediction of ARDS should not only focus on the CA which directly related to its onset. PROM is one of the most important causes of intrauterine infection, the incidence of which is approximately 5–10%.[26] Due to the simple and accurate diagnostic method, PROM is not easily missed, and may be more suitable as an early predictor of neonatal ARDS.

The third independent predictor of neonatal ARDS in our study was the presence of an infectious disease of mother within 7 days before delivery. According to a meta-analysis, the morbidity of early-onset neonatal infection was high among newborns with mothers who had signs of a bacterial infection or colonisation.[27] Group B streptococcus (GBS) is the most common

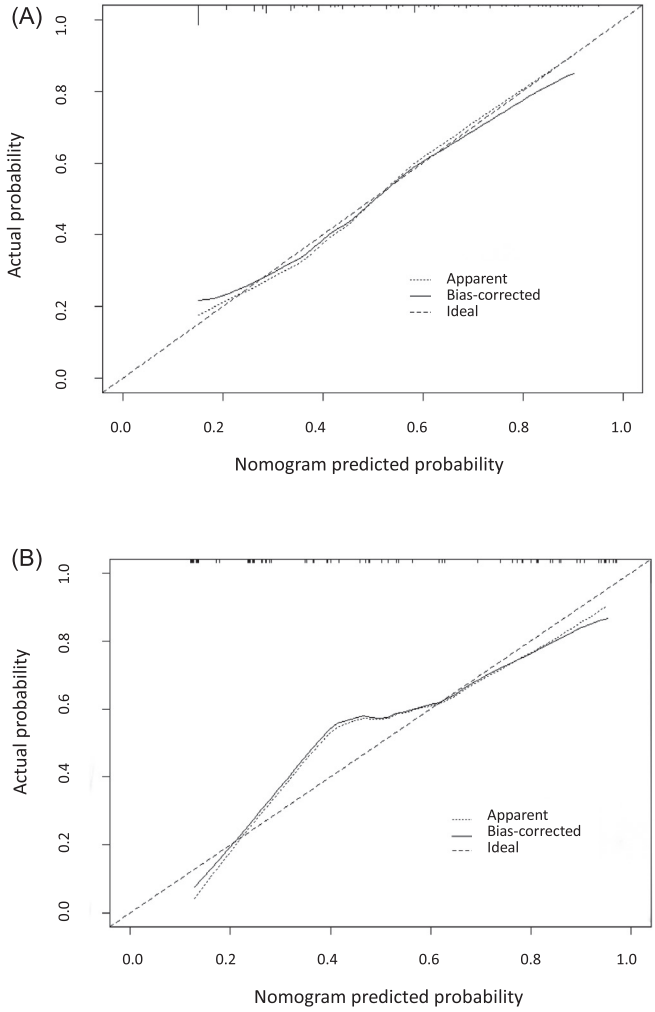

Figure 4. Calibration curve for predicting probability of neonatal ARDS. (A) Training cohort. (B) Validation cohort. ARDS = acute respiratory distress syndrome.

cause of early neonatal infection.[28] There are many adverse outcomes for newborns if mothers are infected with GBS late in their pregnancy.[29] Yu et al. reported that 37·3% infants got pneumonia, 26·8% developed respiratory failure requiring ventilator support, and 12·6% received surfactant within 7 days after birth due to GBS infection.[29] In addition, abnormal vaginal discharge in pregnancy was also a risk factor for PROM,[26] and aerobic vaginitis in late pregnancy was linked to a higher incidence of PROM.[30] Our study found that the proportion of mothers with infectious disease within 7 days before delivery in the ARDS group significantly increased; this result could be related to the increased risk of PROM and intrauterine infection during late pregnancy.

Hospital level was also an independent predictor of neonatal ARDS and was included in our predictive model. Our results suggested that newborns whose mothers received antenatal care in lower-level hospitals were more likely to develop ARDS. In China, maternal and child health hospitals (MCHHs) are special medical institutions which provide health care services for women and children,[31] and many pregnant women tend to choose MCHHs for their antenatal care or delivery. However, district- and county-level MCHHs account for most of the total MCHHs, the efficiencies of which are low.[32] This may be linked to the fact that district- and county-level MCHHs are primary hospitals, there are few skilled medical staff and highly-educated medical workers in primary hospitals, and medical resources are unevenly distributed across primary hospitals and tertiary hospitals.[32,33] A study in Maryland also demonstrated that poor clinical care quality led to an increase in severe maternal morbidity.[34] Therefore, to reduce the morbidity and mortality of neonatal ARDS, it is important to improve the medical services

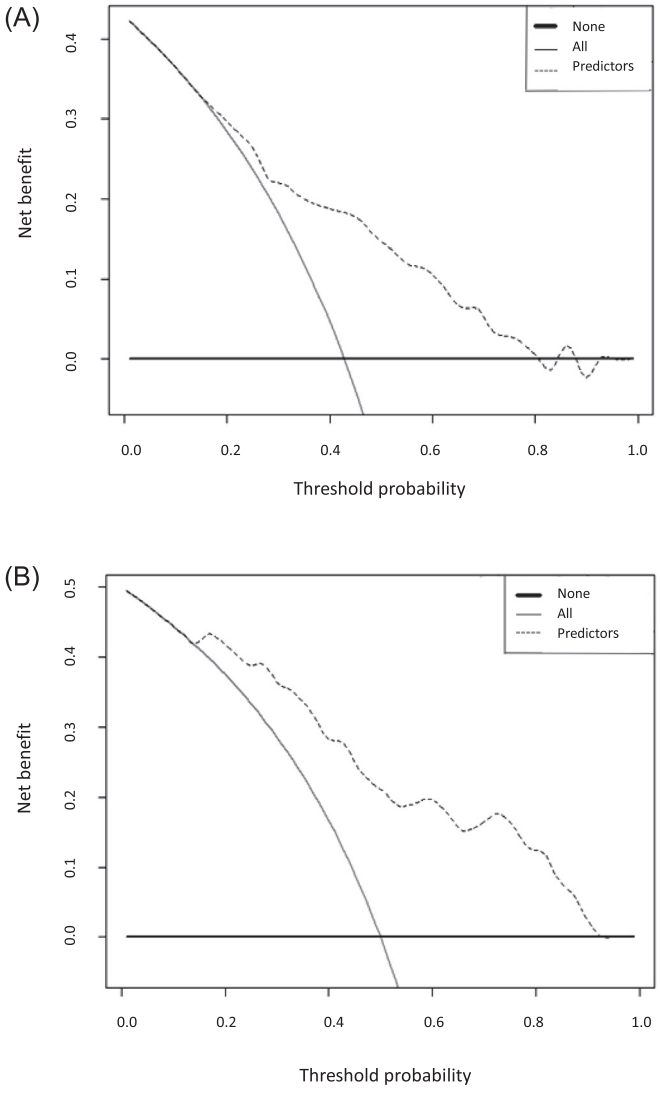

Figure 5. Decision curve analysis in prediction of neonatal ARDS. (A) Training cohort. (B) Validation cohort. ARDS = acute respiratory distress syndrome.

of lower-level hospitals, and establish referral systems and programs for critical pregnant women and high-risk infants.

The Apgar score is internationally recognized as one of the most convenient and acceptable methods for assessing the status of newborns after birth.[35] Apgar score at 1 min does not predict individual outcomes,[35] but a low score at 5 min is associated with neonatal mortality and organ dysfunction.[36–38] In addition, a low Apgar score at 5 min is significantly associated with long-term respiratory disease in children and adolescents.[39] Thus, we included the Apgar score at 5 min as a screening variable for the perinatal prediction of neonatal ARDS, and results showed that the Apgar score at 5 min was negatively correlated with the nomogram points, indicating that the lower the Apgar score, the higher the risk of neonatal ARDS. Low Apgar score indicates that hypoxemia, hypercapnia, and organ dysfunction may occur in newborns.[35,40] In order to ensure the blood flow to important organs such as the heart and brain, blood in the body is redistributed, and the vasculature of non-vital organs such as the lung and intestine is vasoconstricted, reducing blood flow. As one of the most vulnerable organs, the lungs may suffer from varying degrees of injuries, such as respiratory distress, pulmonary haemorrhage, persistent pulmonary hypertension, and even respiratory failure.[38]

In this study, we assessed the perinatal predictors of ARDS in late-preterm and full-term infants and built a

risk prediction model for the early prediction and intervention of ARDS in late-preterm and full-term infants who experienced dyspnoea within 24 h after birth and required mechanical ventilation for the first time. Our external validation confirmed the good accuracy and conformity of the model, alongside its net benefit. The visual and personalized model, that is the nomogram, provides clinicians with a simple and intuitive tool for practical prediction. However, there are several limitations to our study. First, although the diagnosis of neonatal ARDS is not limited by GA,[1] only patients with GA from 34 to 42 weeks were enrolled in our study. This was done as such because preterm infants under 34 weeks are prone to RDS, and, so far, there remain no clear diagnostic criteria to define RDS combined with ARDS. Meanwhile, no cases with GA $\geq$ 42 weeks were identified during this study period. Second, a degree of internal bias of this study is inevitable due to its nature as a retrospective analysis. Third, neonatal ARDS is a relatively new concept, and clinicians lack a deep understanding of neonatal ARDS. In this retrospective study, some potentially meaningful predictors, such as white blood cell, IL-6, TNF-α, umbilical cord blood gas or first hour blood gas, maternal occupation, maternal income, and maternal BMI, among others, were not assessed due to the lack of data. In a further study, we will assess more potential indicators combined with clinical characteristics to build a more accurate prediction model for neonatal ARDS, seeking to reduce neonatal mortality. Fourth, the samples from the training and validation cohorts could only be considered representative of the population of southwest China; therefore, we will seek to carry out an external validation assessment in a multi-centre study.

In conclusion, in this study, we found that mother's education level, PROM, infectious disease within 7 days before delivery, hospital level, and Apgar 5-min score were predictors of neonatal ARDS in late-preterm and full-term infants who experienced dyspnoea within 24 h after birth and required mechanical ventilation. Based on these perinatal predictors, we built a perinatal prediction nomogram for the early prediction of neonatal ARDS, and our external validation confirmed that this model was good. For each patient, higher total points reflected a greater risk of neonatal ARDS. The visual and personalized model of perinatal predictors provides clinicians with a simple and intuitive tool for the early detection and identification of neonatal ARDS, which may be of significance in the fight to reduce the high mortality rates linked to neonatal ARDS.

Contributors

HL conceptualised and designed the study, collected and analysed data, checked literature, and drafted the manuscript. JL and JG contributed to data collection, statistical analysis and literature review. YS interpreted data and checked literature. LW conceptualised and designed the study, drafted the manuscript and implemented the study. HL, JL, JG and LW verified the underlying study data. All authors had full access to all the data in the study and accept responsibility to submit for publication. All authors revised the manuscript and approved the final manuscript as submitted.

Data sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Declaration of interests

None of the authors have conflicts of interest to disclose. None of the authors have financial relationships relevant to this article to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101523.

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