

Risk factors for mortality in neonatal ARDS: a multicenter retrospective cohort study in China

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Abstract As a life-threatening respiratory syndrome, epidemiological data from China has shown that the mortality rate of neonatal acute respiratory distress syndrome (ARDS) is as high as 12.5%. Nevertheless, studies on the influencing factors of this mortality remain limited. This research enrolled newborns with ARDS who initiated invasive mechanical ventilation (IMV) within 72 hours after birth. A Cox regression model with hazard ratio (HR) was constructed using the least absolute shrinkage and selection operator analysis with the lambda.1se screening criterion. Four characteristic variables were identified: inhaled nitric oxide (iNO), high frequency ventilation (HFV), gestational age (GA), and IMV duration. The Kaplan–Meier curve indicated that infants with a higher GA, receiving iNO, or undergoing HFV had a higher risk of death. Restricted cubic spline analysis further revealed that $GA \geq 38.785$ weeks and IMV duration < 117 hours were associated with a significant mortality risk. A linear trend test confirmed a significant linear relationship between GA and mortality risk. Significant interaction effects were observed between “iNO” and “IMV” as well as between “HFV” and “GA”. This study underscores that neonates with advanced GA who require concomitant HFV and iNO therapy are associated with a significantly heightened mortality risk.

Keywords acute respiratory distress syndrome; newborns; prognosis; death; risk factor

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by acute respiratory failure triggered by diverse pathological stimuli. In neonates, a distinct phase of human development, the etiology of ARDS differs markedly from that observed in older children and adults. Both pulmonary factors (severe pneumonia, meconium aspiration syndrome (MAS)) and extrapulmonary factors (severe perinatal sepsis, asphyxia) represent critical and unique etiologies of neonatal ARDS [1]. Neonates' poor environmental adaptability, underdeveloped organs, and immature immune function pose significant challenges in preventing the progression of this disease. Research indicates that in adult ARDS, hospital mortality rates are 34.9% (95% confidence interval (CI) 31.4%–38.5%) for mild cases, 40.3% (95%

CI 37.4%–43.3%) for moderate cases, and 46.1% (95% CI 41.9%–50.4%) for severe cases [2]. In the context of neonatal ARDS, limited epidemiological data from a Chinese multicenter study indicated that the mortality rate reaches as high as 12.5% (40/319) [3]. Therefore, the identification of risk factors proves crucial for evaluating disease severity and predicting mortality risk in neonatal ARDS patients.

So far, comprehensive data on the epidemiology, recognition, management strategies, and clinical outcomes of ARDS patients remain scarce, especially for neonates. The Montreux criteria, a newly established and internationally recognized diagnostic framework, underscore the multifactorial etiology of neonatal ARDS. This encompasses both pulmonary factors (such as pneumonia) and extrapulmonary triggers (like sepsis) [4]. This etiological complexity poses significant challenges to accurate diagnosis, personalized treatment, and reliable prognostic evaluation. Although limited in number, existing studies have reported a significant increase in the expression of inflammatory factors, such as neutrophils and interleukins, in newborns with ARDS [5]. This

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finding strongly suggests that the acute inflammatory response and immune mechanism play crucial roles in the pathogenesis of ARDS. This key feature differentiates ARDS from other common neonatal respiratory disorders, including respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN). Currently, neonatal ARDS lacks effective specific therapies. Standard interventions for neonatal ARDS encompass assisted ventilation, circulatory support, and antimicrobial therapy. Among these, exogenous surfactant administration stands as one of the limited evidence-based treatments [6]. Nevertheless, these therapeutic approaches sometimes prove insufficient, especially in severe cases marked by a high oxygenation index (OI). Consequently, extracorporeal membrane oxygenation (ECMO) has emerged as the last-resort life-saving measure. Regrettably, the application of this advanced technology remains scarce in developing countries like China.

Neonatal ARDS is characterized by rapid progression and a high mortality rate, yet prior research exploring its risk factors remains limited. Liu *et al.* conducted an in-depth investigation into prenatal factors associated with ARDS onset, identifying maternal education level, premature rupture of membranes (PROM), infectious diseases within 7 days before delivery, hospital level, and 5-min Apgar score as independent predictors of neonatal ARDS in late-preterm and full-term infants [7]. Meanwhile, Wu *et al.* reported that the OI and base excess derived from blood gas analysis within 12 hours after birth can serve as predictors of adverse outcomes in newborns receiving non-ECMO treatment for ARDS [8]. These findings highlight the association between early postnatal arterial blood gas (ABG) abnormalities and ARDS severity, underscoring the critical roles of prenatal and perinatal factors in disease pathogenesis and prognosis.

However, to date, research investigating risk factors associated with mortality in neonatal ARDS remains limited, particularly within large-population studies. Given the above, this study is among the first to investigate mortality risk factors in neonates with ARDS using a multicenter database in China.

Materials and methods

This research was a retrospective multicenter case-control study.

Data sources

The dataset was derived from the multicenter retrospective study program conducted by the Jiangsu Provincial Neonatal Respiratory Failure Collaboration Network (JSNRFCN) (ISRCTN registration number:

13622464). Since 2019, 30 neonatal intensive care units (NICUs) across 13 cities in Jiangsu Province have contributed to JSNRFCN by systematically summarizing and uploading standardized data of infants born at gestational ages (GAs) between 23⁺⁵ and 41⁺⁶ weeks. Participants were selected from all infants admitted to the JSNRFCN between January 2019 and December 2022.

Participants

Inclusion criteria: the study enrolled newborns diagnosed with ARDS who exhibited dyspnea following birth, had a GA of at least 34 weeks, and initiated IMV within 72 hours postpartum.

Exclusion criteria: infants with severe congenital malformations or hereditary metabolic diseases were excluded. Neonates diagnosed solely with RDS, pneumonia, TTN, pneumothorax, pleural effusion, or extrapulmonary conditions were also excluded. Additionally, newborns with incomplete key information in the case report form (CRF) or those transferred to centers outside JSNRFCN were excluded.

Grouping: in this study, newborns were categorized into a survival group and a death group based on in-hospital mortality following ARDS diagnosis [4].

Study objective: the main objective is to explore the in-hospital mortality risk factors for ARDS in infants with GA > 34 weeks.

Sample size estimation

As previously reported in a retrospective study, the mortality rate among infants with ARDS was approximately 19.08% (99 of 519) [9]. Building on this prior research, we adopted a comparable mortality rate and conducted power calculations using the “survival” R package. The expected hazard ratio (HR) was set at 1.5, with an anticipated inclusion of 7 variables (6 independent variables and the intercept). The significance level (α) was set at 0.05, and the power ($1-\beta$) was set at 0.80. The estimated sample size required to achieve these parameters was 309 cases, with an expected 59 events. Considering a potential dropout rate of 10%, the total required sample size was calculated to be at least 345 cases.

Clinical data

Definition of neonatal ARDS: in this study, ARDS was diagnosed according to the Montreux definition of neonatal ARDS [4]. This definition encompasses five criteria: timeframe, exclusion criteria, lung imaging, origin of edema, and OI [4].

Clinical data collection: clinical variables were collected with reference to prior studies [7,10] and

clinical experience. It mainly included home address (urban or rural areas), maternal age, maternal hypertension, maternal diabetes, delivery mode, placental disorders, amniotic fluid turbidity, prenatal fever, birthweight, GA, sex, neonatal resuscitation in delivery room (DR), Apgar score, PROM, intubation time, IMV (including high frequency ventilation (HFV) mode and conventional mechanical ventilation (CMV) mode), inhaled nitric oxide (iNO), postnatal ABG, postnatal surfactant administration, sepsis, MAS, patent ductus arteriosus (PDA) and persistent pulmonary hypertension of the newborn (PPHN) confirmed by echocardiography, in-hospital mortality, etc. Since ECMO has not been widely implemented in the JSNRFCN, only 2 cases received ECMO therapy during hospitalization. As a result, ECMO therapy was not included as an influencing factor in this study. CRF for the above-mentioned data were collected by two personnel and then verified by a third staff member.

Statistical methods

Statistical analysis was performed using R 4.3.1 software. Variables with more than 30% missing values were excluded from the analysis. For variables with less than 30% missing data, multiple imputation was employed to address the missing values. The “mice” package was utilized to perform multiple imputation ($m = 5$, $\text{maxit} = 50$). The “with” function was then applied to fit the statistical model to each imputed data set, followed by using the “pool” function to combine the results. To compare the survival and death groups, univariate Cox regression analysis was conducted, reporting HRs with 95% CIs. Before variable screening, a correlation matrix was conducted to visualize the correlations and potential multicollinearity among variables. To further mitigate potential multicollinearity and identify significant predictors, least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation was first employed. Continuous and discrete variables were standardized using the “glmnet” package. Model evaluation was conducted using both the LASSO lambda.1se and LASSO lambda.min screening methods. The method that yielded a more parsimonious variable set while maintaining a robust C-index was ultimately chosen. Subsequently, a multivariate Cox regression analysis with forward selection was conducted using variables selected by LASSO regression. A forest plot was generated to visualize the results of the multivariate Cox regression model. Kaplan–Meier (KM) curves with log-rank tests were constructed for each selected variable. Additionally, restricted cubic spline (RCS) analysis and linear trend tests were performed according to the characteristic of each variable. Interaction effects within the Cox regression model were assessed and expressed

multiplicatively. Sensitivity analysis was also conducted to verify the robustness of the Cox regression. A P -value < 0.05 was considered statistically significant.

Results

General information

From January 2019 to December 2022, a total of 1275 newborns with a GA greater than 34 weeks who presented with dyspnea and initiated IMV within 72 hours post-birth were identified in the JSNRFCN. Following screening based on inclusion and exclusion criteria, 494 neonates with ARDS were enrolled in the study. The cohort comprised 427 infants in the survival group and 67 infants in the death group, yielding a mortality rate of 13.56% (Fig. 1). Univariate Cox regression analysis revealed that selective cesarean section, male, and longer duration of IMV were more frequently observed in the survival group. In contrast, intubation in the DR, compression in the DR, HFV, iNO, and MAS were more common in the death group ($P < 0.05$). Both GA and arterial oxygen partial pressure (PaO_2) were lower in the survival group ($P < 0.05$). Conversely, the death group had significantly lower Apgar scores and ABG pH values ($P < 0.05$) (Table 1).

LASSO variables selection and Cox model construction

Before variable screening, a correlation matrix was generated to visualize the interrelationships among variables. Except for the associations between MAS and amniotic fluid turbidity, as well as between Apgar scores and chest compression, no other variables showed significant high correlations (Fig. S1). Then, LASSO was employed for variable selection and reduction of potential multicollinearity (Fig. 2). Model evaluation was conducted using both the LASSO lambda.1se and LASSO lambda.min parameters (Tables S1 and S2). Results indicated that the LASSO lambda.1se screening approach yielded a more parsimonious variable set with a robust C-index compared to the LASSO lambda.min method (lambda.1se, C-index 0.865, number of variables 6; lambda.min, C-index 0.879, number of variables 16) (Table S2). Consequently, Cox regression analysis was further performed based on the variables by lambda.1se screening approach. This initial model incorporated six characteristic variables (iNO, HFV, GA, IMV duration, pH value in ABG, and 1-min Apgar) (Table 2 and Fig. 2). The collinearity among these variables was examined (Table S3). Following this, multivariable Cox regression with a forward selection method was employed to further refine the variable selection. Eventually, 4 significant variables were identified: iNO (HR 5.67, 95% CI

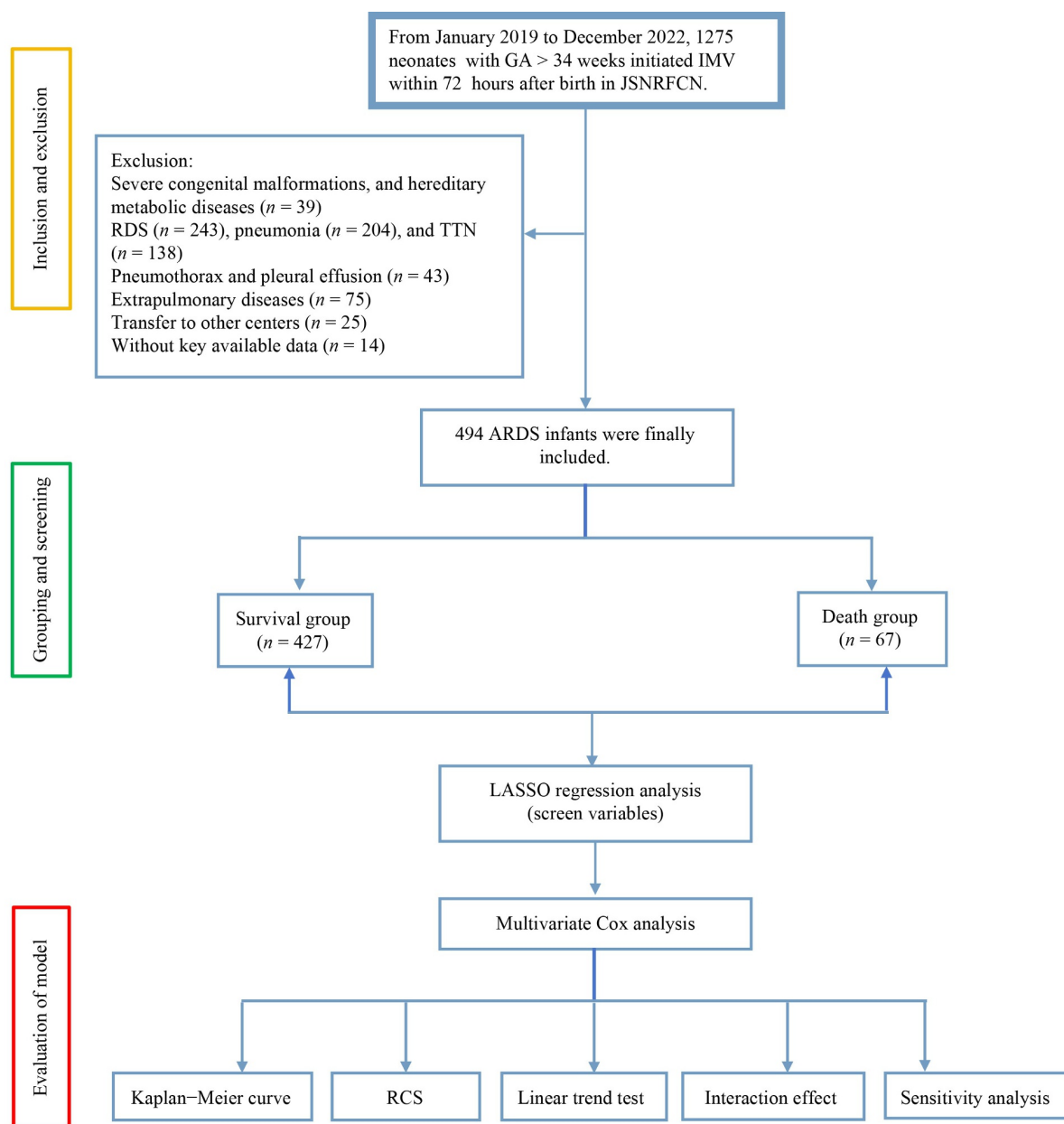


Fig. 1 Flow chart of this study. GA, gestational age; IMV, invasive mechanical ventilation; JSNRFNC, Jiangsu Provincial Neonatal Respiratory Failure Collaboration Network; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn; ARDS, acute respiratory distress syndrome; LASSO, least absolute shrinkage and selection operator; RCS, restricted cubic spline.

3.30–9.76), HFV (HR 1.95, 95% CI 1.13–3.35), GA (HR 1.21, 95% CI 1.04–1.40), and IMV duration (HR 0.97, 95% CI 0.97–0.98) (Table 2 and Fig. 2).

KM curve analysis, RCS, and linear trend test

The KM curve analysis revealed that infants with a lower GA (< 38.785 weeks (median)) or a longer IMV duration (≥ 117 hours (median)) had a higher survival probability (log rank test, $P < 0.05$). In contrast, infants who received iNO therapy or underwent HFV were associated with an elevated risk of mortality (log rank test, $P < 0.05$)

(Fig. S3).

For continuous variables (GA and IMV duration), RCS analysis was performed to further explore their associations. The results indicated that infants with a GA < 38.785 weeks (median) and an IMV duration ≥ 117 hours (median) faced a lower mortality risk (P for overall = 0.013 and < 0.001 , respectively) (Fig. S4). Additionally, a histogram revealed that the majority of deaths (55/67, 82.09%) occurred within the first 117 hours of IMV initiation (Fig. S5). However, the P -value for the nonlinearity of GA in the RCS analysis exceeded 0.05 ($P = 0.373$), suggesting a potential linear relationship

Table 1 Univariate Cox regression analysis between survival group and death group

Variables	Survival group (<i>n</i> = 427)	Death group (<i>n</i> = 67)	<i>P</i>	HR (95% CI)
Maternal characteristics				
Home address (<i>n</i> (%))				
Rural area	233 (54.57%)	43 (64.18%)		1.00 (Reference)
Urban area	194 (45.43%)	24 (35.82%)	0.151	0.69 (0.42–1.14)
Mother age (mean ± SD, year)	29.79 ± 4.87	29.13 ± 4.13	0.297	0.97 (0.93–1.02)
Pregnancy induced hypertension (<i>n</i> (%))				
No	396 (92.74%)	65 (97.01%)		1.00 (Reference)
Yes	31 (7.26%)	2 (2.99%)	0.231	0.42 (0.10–1.73)
GDM (<i>n</i> (%))				
No	359 (84.07%)	59 (88.06%)		1.00 (Reference)
Yes	68 (15.93%)	8 (11.94%)	0.461	0.76 (0.36–1.59)
PROM (<i>n</i> (%))				
No	413 (96.72%)	64 (95.52%)		1.00 (Reference)
Yes	14 (3.28%)	3 (4.48%)	0.635	1.32 (0.42–4.22)
Prenatal fever (<i>n</i> (%))				
No	415 (97.19%)	64 (95.52%)		1.00 (Reference)
Yes	12 (2.81%)	3 (4.48%)	0.429	1.60 (0.50–5.08)
Amniotic fluid turbidity (<i>n</i> (%))				
No	310 (72.60%)	42 (62.69%)		1.00 (Reference)
Yes	117 (27.40%)	25 (37.31%)	0.124	1.48 (0.90–2.42)
Delivery mode (<i>n</i> (%))				
Vaginal delivery	119 (27.87%)	27 (40.30%)		1.00 (Reference)
Selective C-section	226 (52.93%)	26 (38.81%)	0.020	0.53 (0.31–0.91)
Emergency C-section	82 (19.20%)	14 (20.90%)	0.389	0.75 (0.39–1.44)
Neonatal characteristics				
Gestational age (mean ± SD, week)	38.46 ± 1.74	39.06 ± 1.75	0.008	1.22 (1.05–1.42)
Birth weight (mean ± SD, g)	3262.51 ± 589.58	3312.54 ± 598.74	0.463	1.00 (1.00–1.00)
Sex (<i>n</i> (%))				
Female	138 (32.32%)	30 (44.78%)		1.00 (Reference)
Male	289 (67.68%)	37 (55.22%)	0.042	0.61 (0.38–0.98)
Intubation in DR (<i>n</i> (%))				
No	373 (87.35%)	50 (74.63%)		1.00 (Reference)
Yes	54 (12.65%)	17 (25.37%)	0.007	2.13 (1.23–3.69)
Compression in DR (<i>n</i> (%))				
No	402 (94.15%)	57 (85.07%)		1.00 (Reference)
Yes	25 (5.85%)	10 (14.93%)	0.015	2.30 (1.18–4.51)
PS using in DR (<i>n</i> (%))				
No	420 (98.36%)	66 (98.51%)		1.00 (Reference)
Yes	7 (1.64%)	1 (1.49%)	0.955	0.95 (0.13–6.81)
1-min Apgar (median + IQR)	9 (8, 10)	8 (6, 9)	< 0.001	0.85 (0.77–0.93)
5-min Apgar (median + IQR)	9 (8, 10)	9 (7, 10)	0.015	0.86 (0.77–0.97)
Admission age (median + IQR, hour)	2 (1, 7)	2 (1, 10)	0.483	1.01 (0.99–1.03)
Blood gas after birth				
pH (median + IQR, mmHg)	7.32 (7.23, 7.38)	7.22 (7.13, 7.33)	< 0.001	0.05 (0.01–0.22)

(Continued)

Variables	Survival group (n=427)	Death group (n = 67)	P	HR (95% CI)
PaO ₂ (median + IQR, mmHg)	59.42 (48.00, 73.00)	66.40 (52.00, 97.00)	0.008	1.01 (1.01–1.01)
PaCO ₂ (median + IQR, mmHg)	44.05 (37.10, 52.00)	47.32 (40.98, 52.88)	0.134	1.01 (1.00–1.02)
Intubation age (median + IQR, hour)	6 (1.5, 20)	3 (1, 18)	0.461	0.99 (0.97–1.01)
IMV duration (median + IQR, hour)	120 (90, 168)	48 (24, 90)	< 0.001	0.98 (0.97–0.98)
HFV (n (%))				
No	325 (76.11%)	39 (58.21%)		1.00 (Reference)
Yes	102 (23.89%)	28 (41.79%)	0.003	2.07 (1.27–3.36)
iNO (n (%))				
No	319 (74.71%)	32 (47.76%)		1.00 (Reference)
Yes	108 (25.29%)	35 (52.24%)	< 0.001	2.76 (1.71–4.47)
PS using times (n (%))				
0 dose	117 (27.40%)	24 (35.82%)		1.00 (Reference)
1 dose	228 (53.40%)	30 (44.78%)	0.129	0.66 (0.39–1.13)
2 doses	65 (15.22%)	9 (13.43%)	0.279	0.65 (0.30–1.41)
3 doses	17 (3.98%)	4 (5.97%)	0.927	1.05 (0.36–3.03)
PDA (n (%))				
No	340 (79.63%)	50 (74.63%)		1.00 (Reference)
Yes	87 (20.37%)	17 (25.37%)	0.305	1.33 (0.77–2.31)
MAS (n (%))				
No	359 (84.07%)	49 (73.13%)		1.00 (Reference)
Yes	68 (15.93%)	18 (26.87%)	0.040	1.76 (1.03–3.02)
Sepsis (n (%))				
No	211 (49.41%)	42 (62.69%)		1.00 (Reference)
Yes	216 (50.59%)	25 (37.31%)	0.096	1.52 (0.93–2.50)
HIE (n (%))				
No	368 (86.18%)	54 (80.60%)		1.00 (Reference)
Yes	59 (13.82%)	13 (19.40%)	0.243	1.43 (0.78–2.63)

GDM, gestational diabetes mellitus; PROM, premature rupture of membranes; DR, delivery room; PS, pulmonary surfactant; PaO₂, arterial oxygen partial pressure; PaCO₂, arterial carbon dioxide partial pressure; IMV, invasive mechanical ventilation; HFV, high frequency ventilation; iNO, inhaled nitric oxide; PDA, patent ductus arteriosus; MAS, meconium aspiration syndrome; HIE, hypoxic-ischemic encephalopathy; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range.

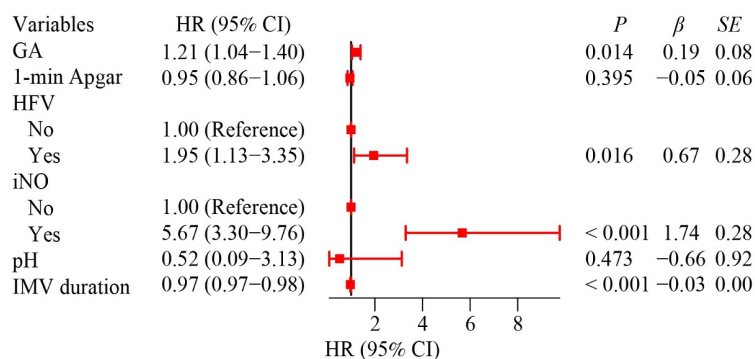


Fig. 2 Forest plot of multivariate Cox regression analysis. GA, 1-min Apgar, pH, and IMV duration were all analyzed as continuous variables. Abbreviations: GA, gestational age; HFV, high frequency ventilation; iNO, inhaled nitric oxide; IMV, invasive mechanical ventilation.

Table 2 Cox regression analysis using variables screened by LASSO lambda.1se

Variables	Univariate					Multivariate ^a				
	β	SE	Z	P	HR (95% CI)	β	SE	Z	P	HR (95% CI)
HFV										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.73	0.25	2.93	0.003	2.07 (1.27–3.36)	0.67	0.28	2.40	0.016	1.95 (1.13–3.35)
iNO										
No					1.00 (Reference)					1.00 (Reference)
Yes	1.02	0.25	4.13	< 0.001	2.76 (1.71–4.47)	1.74	0.28	6.27	< 0.001	5.67 (3.30–9.76)
GA	0.20	0.08	2.63	0.008	1.22 (1.05–1.42)	0.19	0.08	2.46	0.014	1.21 (1.04–1.40)
1-min Apgar	−0.16	0.05	−3.43	< 0.001	0.85 (0.77–0.93)	−0.05	0.06	−0.85	0.395	0.95 (0.86–1.06)
pH	−3.04	0.77	−3.95	< 0.001	0.05 (0.01–0.22)	−0.66	0.92	−0.72	0.473	0.52 (0.09–3.13)
IMV duration	−0.02	0.00	−7.53	< 0.001	0.98 (0.97–0.98)	−0.03	0.00	−8.52	< 0.001	0.97 (0.97–0.98)

^aAdjusted by HFV, iNO, GA, 1-min Apgar, pH, and IMV duration.

Regression analysis was conducted by the forward method.

HFV, high frequency ventilation; iNO, inhaled nitric oxide; GA, gestational age; IMV, invasive mechanical ventilation; SE, standard error; HR, hazard ratio; CI, confidence interval.

(Fig. S4).

Then, a linear trend test was conducted to further assess the above potential linear relationship between GA and mortality risk. The results demonstrated a significant linear relationship after adjusting for various covariates (P for trend < 0.05) (Table 3).

Interaction effect

The interaction effects among variables (iNO, HFV, GA, and IMV duration) in the Cox regression model were evaluated. Significant interaction effects were identified between iNO and IMV duration, as well as between HFV and GA ($P < 0.05$). Of which, in infants with an IMV duration shorter than 117 hours (the median time point), iNO was associated with an increased mortality risk. In addition, in infants with a GA below 38.785 weeks (the median time point), HFV was also associated with an increased probability of mortality (Tables S4–S7).

Sensitivity analysis

Sensitivity analysis was performed using two data subgroups. First, Cox regression was performed on data from infants admitted within 24 hours of birth. Second, Cox regression was conducted on data from infants with a birthweight of ≥ 2500 g. The results showed that the Cox regression models based on these 2 subgroups maintained good robustness and consistency (Concordance: 0.895 and 0.864, respectively) (Table 4).

Discussion

As a common disease, ARDS is a severe respiratory distress syndrome in the NICU, characterized by

persistent hypoxemia, dyspnea, cyanosis, and reduced lung compliance. In China, the incidence of neonatal ARDS is varying from 1% to 5%, with a mortality rate as high as 17% to 24% [11,12]. Although comprehensive epidemiological data remain limited, a regional multicenter study in China has shown that the mortality rate for mild neonatal ARDS is 1.5% (2/133), whereas it surges to 20.4% (38/186) in moderate to severe cases. These findings highlight the critical importance of early identification of high risk factors for neonatal ARDS in improving patient outcomes and reducing mortality [13].

The Montreux diagnostic criteria, specifically formulated for neonates, have gained widespread international adoption [14,15]. However, existing research on risk factors has primarily focused on predictors of ARDS onset rather than mortality. For example, Shen *et al.* developed a risk prediction model using retrospective data from a single NICU ($n = 198$) [10]. They identified calcium levels, platelet count, meconium-stained amniotic fluid, and absolute neutrophil count as effective predictors for neonatal ARDS, with an area under the curve of 0.931. Notably, this study lacked internal or external validation and did not address potential model overfitting [10]. In contrast, De Luca *et al.* conducted an international prospective cohort study and found that indirect-onset neonatal ARDS was strongly associated with infection and prematurity, while direct-onset ARDS was more prevalent in term neonates and linked to perinatal events [12]. These findings highlight that different subtypes of ARDS may arise from distinct etiological triggers. As an acute diffuse inflammatory lung disease, the pathological and physiologic alterations of acute lung injury induced by neonatal ARDS are analogous to the diffuse inflammatory mechanisms observed in pediatric and adult ARDS

Table 3 Linear trend test for gestational age

Variables	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
GA quintile (median)										
36.36 weeks	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
38.00 weeks	1.05 (0.45–2.43)	0.916	1.50 (0.64–3.53)	0.354	1.50 (0.64–3.53)	0.354	1.61 (0.67–3.87)	0.285	1.76 (0.72–4.30)	0.211
39.14 weeks	2.05 (0.94–4.44)	0.070	2.42 (1.11–5.29)	0.027	2.42 (1.11–5.29)	0.027	2.17 (0.98–4.81)	0.056	2.29 (1.03–5.10)	0.042
40.50 weeks	2.31 (1.12–4.78)	0.023	2.69 (1.30–5.58)	0.008	2.69 (1.30–5.58)	0.008	2.61 (1.23–5.53)	0.012	2.57 (1.21–5.45)	0.014
P for trend	0.006		0.003		0.003		0.008		0.011	

Model 1, crude; Model 2, adjusted by HFV; Model 3, adjusted by HFV, iNO; Model 4, adjusted by HFV, iNO, IMV duration; Model 5, adjusted by HFV, iNO, IMV duration, pH, 1-min Apgar.

GA, gestational age; HFV, high frequency ventilation; iNO, inhaled nitric oxide; IMV, invasive mechanical ventilation; HR, hazard ratio; CI, confidence interval.

Table 4 Sensitivity analysis based on multivariate Cox regression

Variables	Model 1 (birthweight \geq 2500 g) ^a					Model 2 (admission age < 24 hours) ^b				
	β	SE	Z	P	HR (95% CI)	β	SE	Z	P	HR (95% CI)
Gestational age	0.19	0.08	2.46	0.014	1.21 (1.04–1.40)	0.17	0.08	2.23	0.026	1.18 (1.02–1.37)
1-min Apgar	−0.05	0.06	−0.85	0.395	0.95 (0.86–1.06)	−0.07	0.06	−1.19	0.236	0.94 (0.84–1.04)
HFV										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.67	0.28	2.40	0.016	1.95 (1.13–3.35)	0.75	0.28	2.67	0.007	2.13 (1.22–3.69)
iNO										
No					1.00 (Reference)					1.00 (Reference)
Yes	1.74	0.28	6.27	< 0.001	5.67 (3.30–9.76)	1.77	0.29	6.16	< 0.001	5.86 (3.34–10.29)
pH	−0.66	0.92	−0.72	0.473	0.52 (0.09–3.13)	−0.36	0.95	−0.38	0.705	0.70 (0.11–4.48)
IMV duration	−0.03	0.00	−8.52	< 0.001	0.97 (0.97–0.98)	−0.03	0.00	−7.93	< 0.001	0.98 (0.97–0.98)
Concordance	0.895					0.864				
SE (concordance)	0.024					0.028				

^aModel 1 was conducted in infants with birthweight \geq 2500 g.

^bModel 2 was conducted in infants with admission age < 24 hours.

HFV, high frequency ventilation; iNO, inhaled nitric oxide; IMV, invasive mechanical ventilation; SE, standard error; HR, hazard ratio; CI, confidence interval.

populations, with comparable clinical manifestations [16]. However, due to the unique physiologic characteristics of neonates, the etiology, treatment approaches, and prognosis of neonatal ARDS differ from those in children and adults [17,18]. The Paediatric ARDS International Epidemiology study has showed that pneumonia or lower respiratory tract infection represents the most prevalent risk factor for pediatric ARDS, followed by non-pulmonary sepsis, whereas aspiration and trauma are less frequently identified as risk factors [19]. In contrast, neonatal ARDS necessitates consideration of unique perinatal risk factors, including both prenatal and postnatal influences. However, current research has primarily centered on identifying factors contributing to ARDS development, while studies specifically addressing key risk factors associated with ARDS mortality remain limited.

In this study, we identified greater GA, NO inhalation, and HFV were potential influencing factors for mortality in neonates with ARDS. Among these, GA emerged as a key perinatal factor. Specifically, infants with a GA below 38.785 weeks exhibited a lower mortality risk (Figs. S3 and S4). Additionally, a significant linear trend was observed between GA and mortality risk (Table 3). A report from Chen *et al.* also indicated that ARDS is most prevalent among neonates with a GA of 37 to 40 weeks, with incidence gradually declining as GA decreases [20]. This phenomenon can be attributed to the fact that ARDS induced by common diseases like MAS, PPHN, and hypoxic-ischemic encephalopathy (HIE) is more common in full-term and post-term babies [21–23]. Ward *et al.* conducted a retrospective cohort study, and found the risk of MAS increased with GA, from 1.3% at 38 weeks to 4.8% at 42 weeks ($P < 0.001$). Compared with term

neonates, premature infants are more susceptible to RDS, and the incidence rate is negatively correlated with GA. The stability of the circulatory system represents another critical factor influencing the outcome of ARDS. Owing to impaired gas diffusion and ventilation disorders in the lungs, coupled with pulmonary arterial hypertension induced by hypoxia and inflammation [24], neonates with ARDS are often accompanied by PPHN. And, iNO has been demonstrated to effectively improve oxygenation in near-term and term neonates with PPHN, reducing the requirement for ECMO therapy [25]. In our study, administration of iNO was strongly associated with an increased mortality risk (Table 2 and Fig. S3). Additionally, a significant interaction effect was observed between IMV and iNO (Tables S5 and S6). This suggests that iNO administration was simultaneously associated with a higher mortality risk. This could be attributed to the fact that these ARDS cases presented with early-stage PPHN while undergoing IMV, indicating a more severe condition. For example, a multicenter, prospective, cross-sectional study in China found that 26% (261/1005) of included ARDS newborns were diagnosed with PPHN [20]. Consequently, ARDS infants receiving iNO treatment for such complications may face a higher risk of death.

ARDS is often characterized by extensive bilateral lung infiltrates, leading to severe gas exchange defects and ventilatory disorders. Our study, through Cox regression analysis, revealed that IMV was associated with a lower mortality rate in patients with ARDS (HR 0.97, 95%CI 0.97–0.98) (Table 2). This finding aligns with clinical logic, as IMV can significantly improve gas exchange disorders in newborns with ARDS. Though prolonged IMV is closely linked to increased mortality (owing to ventilator-induced lung injury, severe infection, and coagulation dysfunction) [26], moderate and appropriately timed IMV remains an effective treatment to improve oxygenation and ventilation. Another notable finding from our RCS analysis is that the majority of deaths occurred within 117 hours (median: 117 hours) of initiating IMV (Figs. S4 and S5). In our opinion, this is likely attributable to the significant inflammatory cytokine storm and the presence of various complications of ARDS, such as PPHN, which are more pronounced in the early stages of the disease, thereby contributing to higher early mortality rates. Hu *et al.* reported that neonates with ARDS were more likely to suffer from early-onset sepsis, PPHN, pulmonary hemorrhage, septic shock, and PDA during the initial phase of the disease ($P < 0.05$) [27]. Although specific neonatal data are limited, pediatric mortality trends reflect similar patterns. Dowell *et al.* reported on 798 pediatric ARDS cases, noting 153 non-survivors (19% mortality). The median time to death was 6 days (interquartile range, 3–13 days) after pediatric ARDS onset [28]. This finding supports the

notion that deaths attributable to ARDS are more prevalent within the first 5–6 days, primarily driven by a spectrum of complications. It is noteworthy that another plausible explanation exists: the association between longer IMV duration and lower mortality may stem from the fact that survivors have more opportunities to continue assisted ventilation. This hypothesis could be further analyzed and validated using a competing risk model in future studies.

However, for specific ARDS subtypes such as severe MAS, chemical inflammation causes acute and diffuse destruction of the alveolar-capillary barrier, ultimately resulting in ARDS [29,30]. In such cases, CMV mode may be suboptimal or fail to achieve satisfactory outcomes. Compared with CMV mode, HFV mode offers advantages such as low tidal volume, low airway pressure, and minimized alveolar injury, making it an ideal lung-protective ventilation strategy. In clinical practice, HFV mode can serve as a first-line approach or a rescue therapy. When HFV is used as the first-choice ventilation strategy, it is typically initiated directly in infants with severe MAS, severe pneumonia, or air leak syndromes. This is in line with the theory that HFV mode could prevent and alleviate ongoing lung injury [31]. In addition to that, HFV is also a life-saving treatment, especially for cases requiring high CMV parameters or demonstrating elevated OIs [32]. Despite this, CMV mode remains the preferred initial strategy for many diseases, such as RDS. In contrast, HFV is adopted as the primary ventilation mode in only a minority of NICUs. However, whether used as salvage therapy or initial ventilation, the role of HFV in neonates remains understudied and warrants further investigation in future research. In our study, through interact analysis we found that HFV was associated with a higher death risk in infants with a GA < 38.785 weeks (Table S4). This might be because that in infants with a GA greater than 38.785 weeks, MAS is a more common etiology of ARDS [21], and HFV is often the preferred first-line and effective ventilation strategy for MAS [33]. However, MAS is relatively rare in newborns with ARDS who have a lower GA [21], and the use of HFV in this population generally serves as salvage therapy rather than the initial treatment of choice. Therefore, the efficacy of HFV appears suboptimal, accompanied by a relatively higher mortality risk. Consequently, the delayed application of HFV mode may indirectly lead to unsatisfactory therapeutic outcomes for neonatal ARDS. Therefore, new challenges have emerged in the respiratory management of neonatal ARDS.

Our study has several limitations that warrant acknowledgment. First, due to its retrospective design, certain clinically relevant variables—including complete blood count, C-reactive protein, procalcitonin, mechanical ventilation parameters, and cardiac ultrasound

measurements—were unavailable and thus excluded from LASSO selection and Cox model construction. Second, it is important to note that the associations between iNO or HFV and increased mortality risks likely reflect the underlying severity of illness in these neonates rather than the treatments themselves. Incorporating comprehensive ventilation parameters, ABG analyses, and cardiopulmonary imaging data would provide a more robust assessment of neonatal cardiopulmonary function and clinical status, enabling more direct identification of mortality-associated risk factors. Third, our cohort lacked infants with ARDS born at a GA < 34 weeks. Additionally, the number of mortality cases—particularly those with prolonged IMV exceeding 117 hours—was relatively limited. This selection bias limits the interpretability and accuracy of the Cox model. Future investigations should include more preterm and low-GA infants to minimize this bias. Fourth, as a rescue therapy [34], ECMO has not yet been widely adopted across the collaborative network. Consequently, ECMO-related data were not included, potentially affecting the assessment of mortality rate and the evaluation of prognostic factors. Given these limitations, future studies in China should adopt a prospective, multicenter design with more comprehensive variable selection to improve the robustness of the findings.

To the best of our knowledge, this is the first time to analyze the mortality risk factors for neonatal ARDS using LASSO and Cox regression in the Chinese population. We identified HFV, iNO, and greater GA as significant predictors of mortality. Moreover, there was a significant interaction effect between “iNO” and “IMV” as well as between “HFV” and “GA”. This study serves as a reminder for neonatologists, particularly in centers where ECMO treatment is unavailable, to promptly identify and address the mortality risk in neonates with greater GA who require both HFV and iNO following birth.

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Compliance with ethics guidelines

Conflicts of interest Yang Yang, Chuchu Guo, Yunsu Zou, Jinxin Shen, Yan Guo, Rui Cheng, Ying Xu, and Xiao Han declare that they have no competing interest.

The study was approved by the ethics committee of the Children's Hospital of Nanjing Medical University (No. NJCH202004037-1) and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed

consent was obtained from all patients for being included in the study.

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