



Newborns with ARDS originating from sepsis of extrapulmonary origin exhibit worse prognoses: findings from a multicenter study in China

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Abstract

Research on the infection-related etiologies of neonatal acute respiratory distress syndrome (NARDS) remains limited. This study aimed to investigate mortality risk differences in NARDS attributed to distinct infection origins (sepsis of extrapulmonary origin or pulmonary infection origin). Subjects were derived from a multicenter retrospective study organized by the Jiangsu Provincial Neonatal Respiratory Failure Collaboration Network. It included neonates with NARDS who initiated invasive mechanical ventilation (IMV) within 72 h of birth. A total of 268 from 1275 NARDS cases with infectious etiologies were enrolled. Multivariate Cox regression found a significant difference in the survival prognosis (sepsis of extrapulmonary origin, adjusted hazard ratio (HR): 3.93, 95% CI 1.79–8.62, log-rank test: $P < 0.001$). Further multi-model and sensitivity analysis confirmed the robustness. Between early-onset and late-onset NARDS, the subgroup analysis showed no significant differences in the mortality risk, whether it was pulmonary infection origin (HR 1.69, 95% CI 0.61–4.64) or sepsis of extrapulmonary origin (HR 0.50, 95% CI 0.17–1.51). Restricted cubic spline also exhibited that the onset time of NARDS was not related to the mortality risk.

Conclusion: This study suggests that for sepsis of extrapulmonary origin, we should be more vigilant about the mortality risk it brings and deal with the risk factors more actively and prudently.

What is Known:

- Limited research has systematically investigated the association between infection origin and mortality risk in neonatal acute respiratory distress syndrome (NARDS).

What is New:

- Our study found that sepsis of extrapulmonary origin was associated with an increased mortality risk in neonates with gestational age > 34 weeks, with robust results from multivariate Cox modeling and sensitivity analyses.
- It highlights the need for heightened vigilance and proactive management of extrapulmonary sepsis-related NARDS to mitigate mortality risk in neonates.

Keywords Acute respiratory distress syndrome · Newborns · Infection · Prognosis · Death

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Abbreviations

ARDS	Acute respiratory distress syndrome
AIC	Akaike information criterion
AFT	Amniotic fluid turbidity
PaO ₂	Arterial partial pressure of oxygen
BIC	Bayesian information criterion
CRF	Case report form
CIs	Confidence intervals
AICc	Corrected AIC
ECMO	Extracorporeal membrane oxygenation
GA	Gestational age
HR	Hazard ratio
HFV	High-frequency ventilation
inhaled NO, iNO	Inhaled nitric oxide
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
JSNRFCN	Jiangsu Provincial Neonatal Respiratory Failure Collaboration Network
KM	Kaplan-Meier
LASSO	Least absolute shrinkage and selection operator
MAS	Meconium aspiration syndrome
NICUs	Neonatal intensive care units
PDA	Patent ductus arteriosus
PPHN	Persistent pulmonary hypertension of the newborn
RCS	Restricted cubic spline
RMSE	Root mean squared error
VIFs	Variance inflation factors

Introduction

Acute respiratory distress syndrome (ARDS) is a critical condition marked by sudden respiratory failure as a result of various pathological triggers. In neonates, the presence of underdeveloped organs, an undermatured immune system, and restricted environmental adaptability pose significant challenges in halting the advancement of this syndrome. Research has indicated that for severe cases of adult ARDS, in-hospital mortality reached 46.1% (95% confidence intervals (CIs), 41.9–50.4%) [1]. Regarding neonatal acute respiratory distress syndrome (NARDS), sparse epidemiological findings from a Chinese multicenter investigation showed a mortality rate of up to 12.5% (40/319) [2]. The underlying causes of NARDS are notably distinct from those seen in older children and adults. Both lung-related issues, such as severe pneumonia and meconium aspiration syndrome (MAS), and non-pulmonary factors, including severe perinatal sepsis and asphyxia, play essential and distinctive roles in the development of NARDS [3].

To date, there remains a scarcity of data concerning the epidemiology, identification, handling, and outcomes of ARDS patients, especially in the neonatal population. The Montreux criteria, a recently established and widely acknowledged diagnostic framework, underscore the intricate nature of NARDS causes [4]. However, the complexity of etiology poses significant challenges for early and precise diagnosis, therapeutic intervention, and prognostic evaluation. Among various contributing factors, existing evidence suggests that a considerable proportion of NARDS demonstrates markedly elevated levels of inflammatory markers, such as neutrophils and interleukins [5]. This observation supports the potential role of acute inflammatory responses and immune mechanisms in the pathogenesis of NARDS.

Nevertheless, limited research has systematically investigated the association between infection origin and mortality risk in NARDS, especially in China. To address this knowledge gap, our study represents the first multicenter analysis conducted in China to evaluate how different sources of infection impact prognosis in NARDS.

Materials and methods

Data source

The data were derived from a multicenter retrospective study organized by the Jiangsu Provincial Neonatal Respiratory Failure Collaboration Network (JSNRFCN) (ISRCTN: 13,622,464). Since its inception in 2019, this network has prospectively gathered standardized clinical records from 30 neonatal intensive care units (NICUs) spanning 13 cities in Jiangsu Province. The study included neonates with gestational ages between 23 + 5 and 41 + 6 weeks who were admitted to JSNRFCN-affiliated NICUs from January 2019 to December 2022.

Participants

- (1) Inclusion criteria: (1) NARDS meeting Montreux diagnostic standards [4]; (2) infection-related NARDS; (3) delivery at 34 weeks' gestation or later; and (4) initiation of invasive mechanical ventilation (IMV) within the first 3 days of life.
- (2) Exclusion criteria: (1) presence of major birth defects (notably severe cardiac abnormalities or chromosomal disorders) or inherited metabolic diseases; (2) diagnosis limited to respiratory distress syndrome (caused by primary surfactant deficiency), mild lung infections, transient tachypnea of the newborn, air leaks, pleural fluid collections, or non-respiratory conditions (e.g., developmental diaphragm abnormalities); (3) inadequate or absent crucial medical information in the case

report form (CRF); (4) transfer to healthcare institutions not participating in JSNRFCN with missing post-transfer data.

- (3) Exposure and grouping: The primary exposure variable was defined as the source of NARDS infection. Based on retrospective analysis, neonates were stratified into two distinct groups (the sepsis of extrapulmonary origin, as sepsis origin group, or the pulmonary infection origin, as pneumonia origin group) according to infection origin [4].

Pulmonary infection here referred to severe pneumonia caused by a variety of pathogenic microorganisms (including bacteria, viruses, fungi, and mycoplasma) [6]. Meconium aspiration, milk aspiration, and blood aspiration were not classified as pulmonary infections in this study. The diagnosis of neonatal sepsis (including septic shock) was based on the Chinese expert consensus on the diagnosis and treatment of neonatal sepsis [7].

- (4) Study endpoints and aims: In-hospital death served as the primary endpoint. This investigation mainly aimed to compare mortality risks during hospitalization between NARDS stemming from sepsis origin versus those with pneumonia origin. In addition, the differences of prognosis between early onset and late onset of ARDS were explored in subgroup analysis.

Sample size estimation

- (1) Based on data from our preliminary investigation of ARDS cases with infectious etiology, we established the following parameters for sample size estimation: (1) The observed mortality rate was 15.0% among neonates with infection-associated NARDS; (2) Sepsis origin demonstrated a significantly higher risk than pneumonia origin (hazard ratio (HR)=3.80).
- (2) Using these parameters in the “survival” package for R, we conducted power calculations with the following specifications: (1) two-tailed significance level (α) of 0.05; (2) statistical power ($1-\beta$) of 80%; (3) anticipated mortality rate of 15.0%. The analysis indicated that a minimum of 231 cases would be required to detect the specified HR. Considering a 10% dropout rate, it is estimated that the sample size should reach at least 254 cases, including 30 deaths.

Clinical data and definitions

- (1) Definition of NARDS: The study employed the Montreux definition [4], an internationally recognized diagnostic standard for NARDS. This validated assessment

tool systematically examines five critical components: temporal parameters, exclusionary conditions, edema etiology, oxygenation index, and radiographic findings [4].

- (2) Clinical data collection: Clinical variables were systematically collected through a standardized CRF. Variables were prioritized based on (1) biological plausibility in NARDS pathophysiology, (2) prior associations with neonatal outcomes in cited literature [8, 9], and (3) availability within the JSNRFCN dataset.

The dataset encompassed the following domains: It mainly included residential area (urban or rural areas), maternal age, maternal hypertension, maternal diabetes, delivery mode, placental disorders, amniotic fluid turbidity (AFT), prenatal fever ($\geq 38^\circ\text{C}$), birth weight, gestational age (GA), sex, neonatal resuscitation in the delivery room, Apgar score, premature rupture of membranes, intubation time, IMV (including high-frequency ventilation (HFV)), inhaled nitric oxide (inhaled NO, iNO), arterial blood gas after birth, surfactant administration after birth, MAS, patent ductus arteriosus (PDA), persistent pulmonary hypertension of the newborn (PPHN) confirmed by echocardiography, death (time-to-event from admission), etc.

Due to the limited availability of extracorporeal membrane oxygenation (ECMO) therapy in Jiangsu Province during our investigation period, merely two patients in our study population underwent this treatment. This extremely small sample size ($n=2$) rendered any statistically significant analysis of ECMO's prognostic value unfeasible. Therefore, to preserve the robustness of our statistical models, ECMO was not included as a variable in multivariate analysis.

- (3) Quality control of collected data: CRF of the above independent data was abstracted by two trained research staff and then cross-checked by a senior clinician.

Statistical methods

All statistical analyses were conducted with R software (version 4.3.1). Missing data were addressed through the random forest algorithm (“missForest” package). Variable selection incorporated three complementary approaches: (1) the least absolute shrinkage and selection operator (LASSO) regression with tenfold cross-validation (“glmnet” package), (2) the Boruta algorithm (a random forest-based feature selection method) (“Boruta” package), and (3) univariate Cox regression with backward elimination (“survival” package). The definitive predictive variables were identified by selecting only those features consistently chosen by all three methods.

These selected variables were subsequently incorporated into a multivariate Cox proportional hazards model to

calculate HRs and corresponding 95% CIs using the “survival” package. The proportional hazards assumption was verified using tolerance, and variance inflation factors (VIFs) were examined to assess multicollinearity (threshold: tolerance > 0.2 and VIF < 5). The evaluation of multivariate Cox regression was used to determine the Akaike information criterion (AIC), corrected AIC (AICc), Bayesian information criterion (BIC), Nagelkerke’s R^2 , and root mean squared error (RMSE). Model robustness was evaluated through multi-model validation. Survival patterns were visualized using Kaplan–Meier (KM) curves with log-rank testing. The E -value for 95% CI was also calculated using the “EValue” package.

Additional analyses included (1) subgroup comparisons between early and late onset ARDS using the onset time median, (2) restricted cubic spline (RCS) modeling (four knots) to assess nonlinear associations between ARDS onset time and mortality (“rms” package), and (3) sensitivity analyses using three distinct sub-cohorts (neonates who died within 10 days of admission; neonates admitted within 24 h of birth). Neonates with septic shock were excluded. All tests employed two-sided significance thresholds ($\alpha=0.05$).

Results

General information of included NARDS infants

During the 2019–2022 study period, the JSNRFN registry identified 1275 neonates > 34 weeks’ GA who received IMV within 72 h of birth. After applying selection criteria, 418 NARDS cases were enrolled (349 survivors, 69 non-survivors; Supplementary Fig. 1 and Supplementary Table 1). Comparative analysis revealed significant between-group differences ($P<0.05$): Survivors had higher rates of selective cesarean section, lower GA, older maternal age, better Apgar score, and longer IMV duration. Non-survivors exhibited elevated arterial partial pressure of oxygen (PaO_2), lower pH, more frequent complications of MAS, PPHN, and/or AFT, and greater utilization of HFV or iNO therapy (Table 1).

The cohort included 268 NARDS infants with infectious etiology (pneumonia origin group, $n=213$; sepsis origin group, $n=55$), of whom 30 died (Supplementary Fig. 1 and Supplementary Fig. 2A–B). Univariate analysis identified several mortality-associated factors (Supplementary Table 2): sepsis origin, gestational maturity, acid–base parameters (pH and PaO_2), duration of IMV, use of HFV and iNO therapy, and complications including PDA and PPHN ($P<0.05$). Demographic data further showed most infants were > 38 weeks’ gestation and had birth weights of 3000–3500 g (Supplementary Figs. 2C–1D).

Variable screening

During variable screening, univariate Cox backward regression identified nine characteristic variables: PPHN (HR = 6.15), infectious disease (HR = 3.93), PDA (HR = 1.76), iNO (HR = 1.50), HFV (HR = 1.28), IMV duration (HR = 0.96), vasoactive drugs (HR = 0.28), AFT (HR = 0.20), and pH (HR = 0.09) (Supplementary Table 2). LASSO regression selected five characteristic variables: PPHN (coefficient = 0.97), infectious disease (coefficient = 0.68), PDA (coefficient = 0.18), iNO (coefficient = 0.10), and IMV duration (coefficient = -0.01) (Supplementary Table 3, Supplementary Figs. 3 and 4). The Boruta algorithm identified four characteristic variables: IMV duration (mean importance score = 27.01), PPHN (mean importance score = 9.79), infectious disease (mean importance score = 6.45), and iNO (mean importance score = 5.72) (Supplementary Table 4).

Collectively, LASSO regression, the Boruta algorithm, and univariate Cox backward regression identified four significant intersecting variables: infection origin and three covariates (PPHN, IMV duration, iNO) (Supplementary Fig. 5).

Prognostic differences between sepsis origin group and pneumonia origin group via multivariate Cox regression

No obvious multicollinearity was observed among the independent variables (Supplementary Table 5 and Supplementary Fig. 6). The evaluation of multivariate Cox regression showed AIC 236.309, AICc 236.461, BIC 242.672, Nagelkerke’s R^2 0.451, root mean square error (RMSE) 0.317. Multivariate Cox regression analysis using the selected intersecting variables revealed a significant survival prognosis difference. NARDS with sepsis origin had a significantly higher mortality risk (adjusted HR = 3.93, 95% CI 1.79–8.62, log-rank test: $P<0.001$) (Fig. 1 and Supplementary Table 6). The KM curve further confirmed that infants with sepsis origin exhibited a higher mortality risk (HR = 3.663, 95% CI 1.787–7.507, log-rank test: $P<0.001$) (Fig. 2).

Four sequential models incorporating varying variable combinations were constructed. All models consistently showed that sepsis origin was associated with significantly higher HRs compared to pneumonia origin ($P<0.01$) (Table 2).

Results showed that sepsis origin was associated with a higher mortality risk compared to pneumonia origin across all subgroups (HR = 3.93, 95% CI 1.79–8.62). Notably, no differences were observed between subgroups for neonatal

Table 1 General information of all NARDS infants by univariate Cox analysis

Characteristic	<i>N</i>	Event <i>N</i>	HR	95% CI	<i>P</i> -value
Home address					
Rural area	243	47	Reference	Reference	
Urban area	175	22	0.63	0.38, 1.05	0.077
GDM					
No	351	61	Reference	Reference	
Yes	67	8	0.68	0.33, 1.42	0.304
Maternal hypertension					
No	386	66	Reference	Reference	
Yes	32	3	0.53	0.17, 1.69	0.283
Mother's age (y)	418	69	0.94	0.89, 0.99	0.022
Prenatal fever					
No	406	66	Reference	Reference	
Yes	12	3	1.65	0.52, 5.26	0.394
PROM					
No	404	66	Reference	Reference	
Yes	14	3	1.35	0.42, 4.30	0.610
AFT					
No	296	41	Reference	Reference	
Yes	122	28	1.70	1.05, 2.75	0.031
Delivery mode					
Vaginal delivery	128	27	Reference	Reference	
Selective C-section	203	26	0.58	0.34, 0.99	0.044
Emergency C-section	87	16	0.86	0.47, 1.60	0.642
Gestational age (weeks)	418	69	1.30	1.12, 1.50	<0.001
Birth weight (g)	418	69	1.00	1.00, 1.00	0.086
Sex					
Male	141	30	Reference	Reference	
Female	277	39	0.63	0.39, 1.02	0.059
Admission age (hour)	418	69	1.00	0.99, 1.02	0.571
Intubation in DR					
No	342	53	Reference	Reference	
Yes	76	16	1.41	0.81, 2.47	0.225
Compression in DR					
No	377	59	Reference	Reference	
Yes	41	10	1.56	0.80, 3.06	0.191
5 min Apgar	417	69	0.90	0.81, 0.99	0.038
Blood gas after birth					
PH	418	69	0.16	0.04, 0.63	0.009
PaO ₂ (mmHg)	418	69	1.01	1.00, 1.01	0.043
PaCO ₂ (mmHg)	418	69	1.01	1.00, 1.02	0.094
Intubation time (hour)	418	69	0.99	0.97, 1.01	0.277
IMV duration (hour)	418	69	0.98	0.98, 0.99	<0.001
HFV					
No	302	39	Reference	Reference	
Yes	116	30	2.11	1.31, 3.40	0.002
NO inhalation					
No	290	36	Reference	Reference	
Yes	128	33	2.14	1.33, 3.43	0.002
Surfactant using times					
0 dose	155	31	Reference	Reference	
1 dose	193	28	0.70	0.42, 1.17	0.171

Table 1 (continued)

Characteristic	N	Event N	HR	95% CI	P-value
2 doses	52	7	0.62	0.27, 1.40	0.248
3 doses	18	3	0.76	0.23, 2.49	0.648
Vasoactive drugs					
No	73	8	Reference	Reference	
Yes	345	61	1.63	0.78, 3.41	0.193
Air leak					
No	364	60	Reference	Reference	
Yes	54	9	0.97	0.48, 1.96	0.937
PDA					
No	334	50	Reference	Reference	
Yes	84	19	1.60	0.94, 2.71	0.082
MAS					
No	354	51	Reference	Reference	
Yes	64	18	2.06	1.20, 3.53	0.008
PPHN					
No	263	27	Reference	Reference	
Yes	155	42	2.77	1.71, 4.50	<0.001
HIE					
No	364	56	Reference	Reference	
Yes	54	13	1.59	0.87, 2.91	0.131
IVH					
No	414	68	Reference	Reference	
Yes	4	1	1.37	0.19, 9.90	0.753

Abbreviation: *GDM* gestational diabetes mellitus, *AFT* amniotic fluid turbidity, *PaO₂* arterial oxygen partial pressure, *PaCO₂* arterial carbon dioxide partial pressure, *IMV* invasive mechanical ventilation, *HFV* high frequency ventilation, *NO* nitric oxide, *PS* pulmonary surfactant, *DR* delivery room, *PROM* premature rupture of membranes, *HFV* high frequency ventilation, *PDA* patent ductus arteriosus, *MAS* meconium aspiration syndrome, *PPHN* persist pulmonary hypertension in newborns, *HIE* hypoxic-ischemic encephalopathy, *IVH* intraventricular hemorrhage, *HR* hazard ratio, *CI* confidence interval

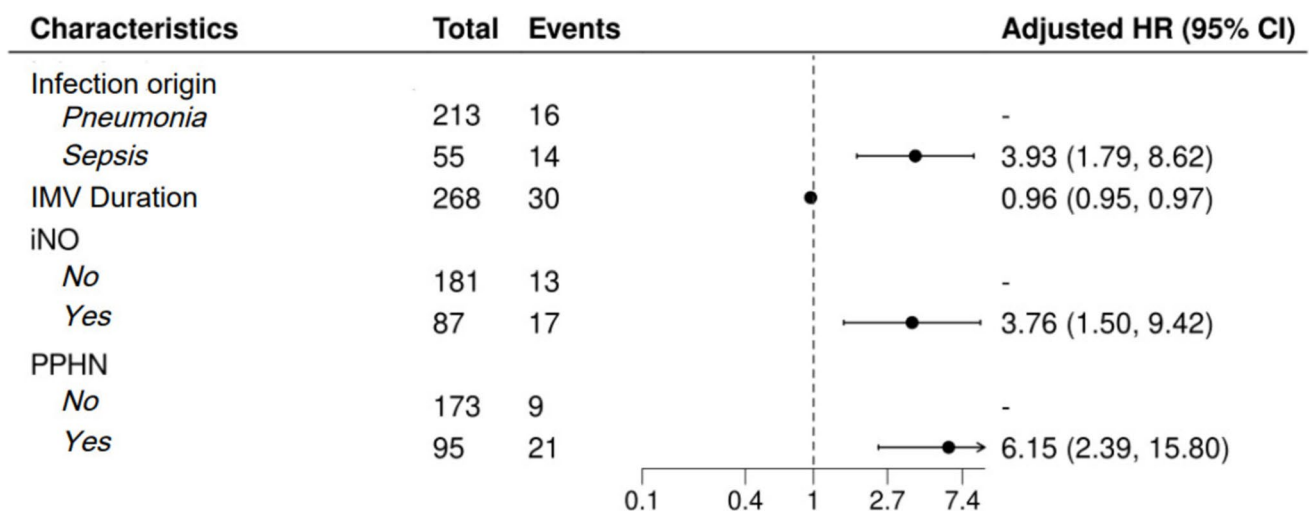


Fig. 1 Forest plot of multivariate Cox regression analysis (Abbreviations: IMV, invasive mechanical ventilation; NO, nitric oxide; PPHN, persistent pulmonary hypertension of the newborn)

ARDS with pneumonia or sepsis origins ($P > 0.05$) (Supplementary Table 7).

Subgroup analysis of early- vs. late-onset NARDS with pneumonia or sepsis origins

Subgroup analysis revealed no significant mortality risk differences between early-onset and late-onset NARDS, regardless of infection origin: pneumonia (HR = 1.69, 95% CI 0.61–4.64) and sepsis (HR = 0.50, 95% CI 0.17–1.51) (Supplementary Tables 8 and 9).

RCS analysis further confirmed no association between NARDS onset timing and mortality risk: for pneumonia origin (P for overall trend = 0.802, P for nonlinearity = 0.773); for sepsis origin (P for overall trend = 0.252, P for nonlinearity = 0.134) (Supplementary Fig. 7).

Sensitivity analysis of the Cox regression model in NARDS with pneumonia or sepsis origins

Sensitivity analysis was performed using three sub-datasets. First, Cox regression on infants admitted within 24 h of birth

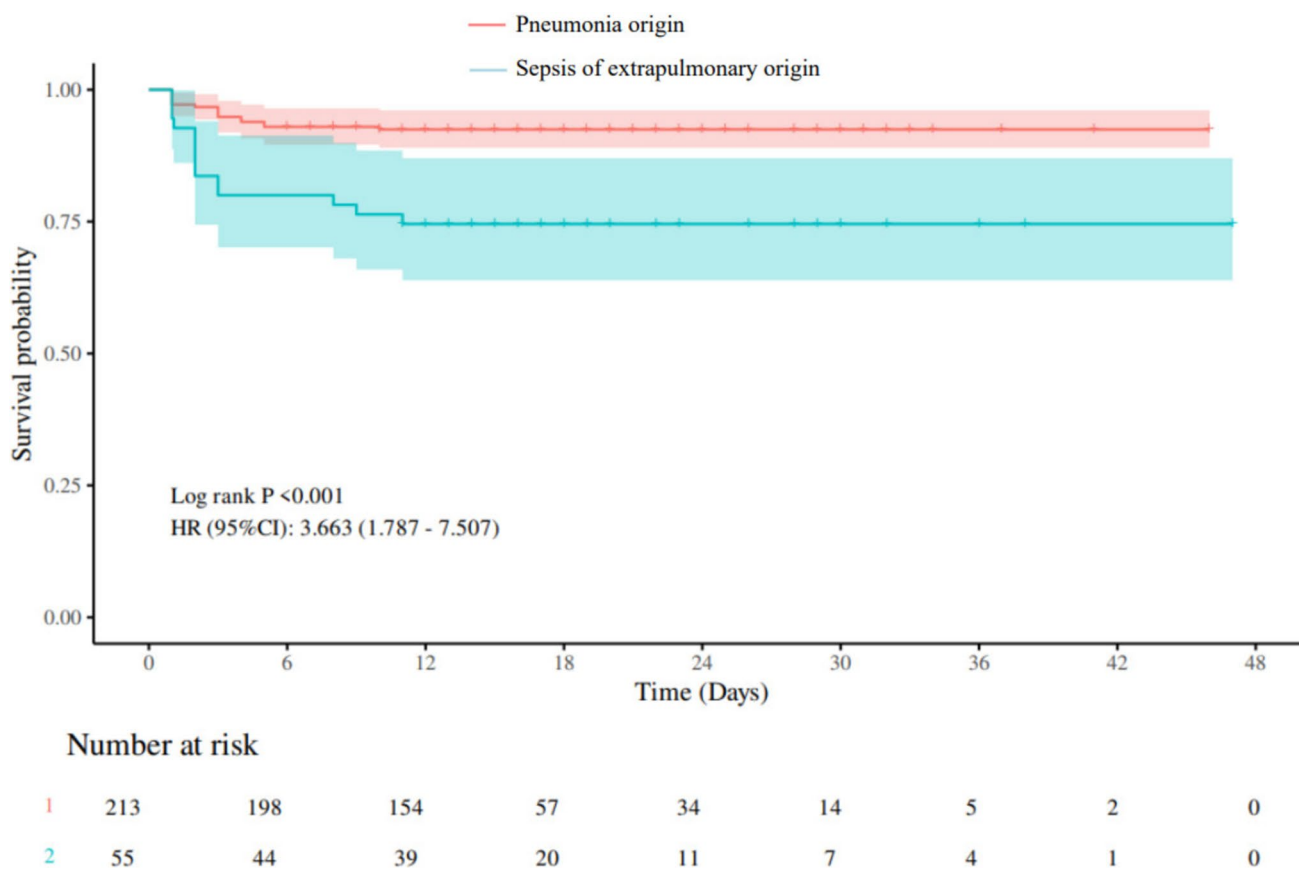


Fig. 2 The Kaplan–Meier curve with log-rank test

Table 2 Multi-model analysis of the Cox model

Variables	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P	Model 3 HR (95% CI)	P	Model 4 HR (95% CI)	P
Pneumonia origin	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Sepsis origin	3.66 (1.79 ~ 7.51)	<.001	3.66 (1.79 ~ 7.51)	<.001	2.63 (1.24 ~ 5.57)	0.012	3.93 (1.79 ~ 8.62)	<.001

Model 1: Crude; Model 2: Adjusted by nitric oxide inhalation; Model 3: Adjusted by nitric oxide inhalation and persistent pulmonary hypertension in newborns; Model 4: Adjusted by nitric oxide inhalation, persistent pulmonary hypertension in newborns, and invasive mechanical ventilation duration

Abbreviation: *HR* hazard ratio, *CI* confidence interval

yielded an HR of 4.48 (95% CI 2.01–10.03, *E*-value 8.43) for sepsis origin (Table 3). Second, analysis of 10-day mortality after NARDS onset also showed a higher HR for sepsis origin (HR = 3.94, 95% CI 1.79–8.65, *E*-value 7.34) (Table 3). Third, newborns with septic shock were excluded. Then, the sepsis origin showed a higher HR (5.14, 95% CI 1.96–13.49) with *E*-value 9.75 (Table 3).

Discussion

Characterized by acute lung inflammation, NARDS is driven by the infiltration of inflammatory cells, pro-inflammatory cytokines, and pathogens. This widespread inflammation injures the alveolar-capillary membrane, which in turn increases permeability, causes pulmonary edema, and culminates in diffuse alveolar damage [10].

The inflammatory cascade in NARDS is precipitated by a variety of direct pulmonary or indirect systemic insults. In this study, based on multivariate Cox regression analysis, neonates with sepsis-origin NARDS demonstrated significantly higher mortality risk compared to those with pneumonia-origin NARDS (adjusted HR = 3.93, 95% CI 1.79–8.62). This association remained consistent across sequentially adjusted models and subgroup analyses of early- versus late-onset NARDS. Sensitivity analyses further confirmed the robustness of the findings, with sepsis origin consistently associated with elevated mortality risk in various sub-datasets.

The incidence of NARDS varied among different centers and countries. In a multicenter study, 15,916 neonates were admitted to the NICUs, resulting in a NARDS prevalence of 1.5% overall. The prevalence varied among participating centers, ranging from 1 to 5% [11]. Moreover, global data indicate a considerable case fatality rate for the condition,

reaching 17 to 24% [11, 12]. Although comprehensive epidemiological data remain limited in China, a regional multicenter study reported a mortality rate of 20.4% (38/186) among moderate-to-severe NARDS patients [2]. Thus, early identification of high-risk factors for NARDS is critical for improving patient outcomes and reducing mortality.

As an acute diffuse inflammatory lung disease, NARDS shares pathological and physiological characteristics of acute lung injury with pediatric and adult ARDS, including a similar underlying mechanism of diffuse inflammation and clinical manifestations [13]. However, the etiology, treatment, and prognosis of NARDS differ significantly from those in older populations due to the unique physiological characteristics of neonates [14, 15]. Since 2017, the Montreux diagnostic criteria—specifically developed for neonates—have been widely adopted globally [16, 17]. Using these criteria, De Luca et al. conducted an international prospective cohort study and found that direct-induced NARDS like aspiration had lower mortality than indirect-induced NARDS. And sepsis was the most common trigger of NARDS, with indirect-onset (extra-pulmonary) NARDS predominantly associated with infection [12]. In neonates, infection-related NARDS can be subclassified into intrapulmonary (e.g., severe pneumonia caused by bacteria, viruses, or mycoplasma [18, 19]) and extrapulmonary (e.g., sepsis or septic shock from non-pulmonary infections [20]) origins. However, the difference in mortality risk between pulmonary infection and sepsis of extrapulmonary origin-related NARDS remains unclear.

This study is to demonstrate that neonates with sepsis of extrapulmonary origin-related NARDS had a significantly higher mortality risk (adjusted HR = 3.93, 95% CI 1.79–8.62), a finding validated by multi-model analysis and KM curve. In this study, pulmonary infection-related NARDS was defined as infectious severe pneumonia, while systemic infection-related NARDS referred to sepsis from

Table 3 Sensitivity analysis for infants with NARDS using multivariate Cox regression

Characteristic	<i>N</i>	Event <i>N</i>	HR	95% CI	<i>E</i> -value for CI	<i>P</i> -value
ARDS reason ^a						
Pneumonia origin	189	14	Reference	Reference		
Sepsis origin	52	14	4.48	2.01, 10.03	8.43	<0.001
ARDS reason ^b						
Pneumonia origin	213	16	Reference	Reference		
Sepsis origin	55	14	3.94	1.79, 8.65	7.34	<0.001
ARDS reason ^c						
Pneumonia origin	213	16	Reference	Reference		
Sepsis origin	23	11	5.14	1.96, 13.49	9.75	<0.001

Abbreviation: *IMV* invasive mechanical ventilation, *NO* nitric oxide, *PPHN* persist pulmonary hypertension of the newborn, *HR* hazard ratio, *CI* confidence interval

^aAdmission within 24 h of birth

^bMortality within the first 10 days

^cPatients with septic shock were excluded

extrapulmonary sources. Intuitively, sepsis implies a severe systemic infection, leading to more profound organ dysfunction [21]. Sepsis is predominantly caused by gram-negative (with endotoxin lipopolysaccharide in the cell wall) or gram-positive (with exotoxin lipoteichoic acid) bacteria [22]. Bacterial components and toxins trigger a cascade of inflammatory responses via immune cells, leading to cytokine storms (e.g., activation of interleukins, chemokines, tumor necrosis factor, and interferon) [23]. This results in microvascular thrombosis, leukocyte adhesion, vascular hyperpermeability, and subsequent hypoperfusion and multi-organ dysfunction [21]. Although severe pneumonia directly impairs alveolar ventilation and gas exchange, its systemic adverse effects are less pronounced and delayed compared to sepsis of extrapulmonary origin.

Although the mortality rate of NARDS originating from sepsis is significantly higher than that originating from pulmonary infection, it remains unknown whether there are differences in the early and late onset of the infection. From further subgroup analysis, it was found that there was no significant difference in the mortality risk between early-onset and late-onset NARDS, whether it was pneumonia origin or sepsis origin (Supplementary Tables 8 and 9, and Supplementary Fig. 7). Vincent et al. found ARDS patients with late-onset ARDS (after 48 h of intensive care unit (ICU) admission) had longer hospital lengths of stay than patients with early-onset ARDS (within 48 h of ICU admission). ICU and hospital mortality rates were lower in late-onset ARDS than in early-onset ARDS, but these differences were not statistically significant [24]. Fuchs et al. included a total of 1411 ventilated patients: 41% had ARDS on admission (as early-onset), and 28.5% developed ARDS during their ICU stay (as late-onset). They found the 28-day mortality between early- and late-onset ARDS did not show significant differences [25]. In contrast, Zhang et al. conducted a multicenter study. They found late-onset moderate to severe ARDS patients had both shorter survival time and higher mortality rate in 28-day (odds ratio = 1.46, 95% CI 1.04–2.06, $P=0.0305$) and 60-day (odds ratio = 1.44, 95% CI 1.03–2.02, $P=0.0313$) observations [26]. In our view, the above contradictory conclusions may stem from differences in the etiological composition of ARDS across study populations or variations in ARDS definition criteria. In fact, NARDS exhibits marked heterogeneity in its triggers. Loi et al. conducted a prospective observational study and found that the NARDS group demonstrated substantial global interpatient aeration heterogeneity through lung ultrasound. Notably, this heterogeneity differed among NARDS patients based on their specific triggers (overall $P=0.044$) [27]. Such heterogeneity in NARDS indicates that the condition can no longer be considered a single disease entity. Instead, it represents a common endpoint resulting from a spectrum of distinct pathological processes. Given this heterogeneity in

etiologies, there is a need to classify and subtype NARDS—shifting the clinical paradigm from “managing NARDS as a uniform condition” to “treating specific NARDS subtypes.” This shift is critical to advancing precision medicine in the care of patients with ARDS.

Limitations

This study has several limitations. First, due to its retrospective design, key infection-related variables (e.g., complete blood count, C-reactive protein, procalcitonin) were incompletely collected for further analysis. Second, only in-hospital mortality was assessed, with no follow-up data on post-discharge outcomes. In addition, the number of deaths and cases of sepsis of extrapulmonary origin was relatively small. It would bring selective bias and insufficient statistical power to some extent. Third, we did not evaluate prognosis differences in pathogen types (e.g., bacterial vs. viral infections or bacterial virulence). Fourth, demographic disparities between groups were present, and while statistical corrections were applied, baseline data were not fully matched. Future prospective multicenter studies in China with comprehensive variable inclusion are warranted to address these gaps.

Conclusion

To our knowledge, this is the first study to analyze mortality risk differences between pulmonary infection origin and sepsis of extrapulmonary origin in NARDS in China. We found that sepsis origin significantly increased mortality risk in the neonates with GA > 34 weeks, with robust results from multivariate Cox modeling and sensitivity analyses. Notably, no mortality differences were observed between early- and late-onset NARDS induced by infection. These findings highlight the need for heightened vigilance and proactive management of sepsis of extrapulmonary origin-related NARDS to mitigate mortality risk in neonates.

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Authors' contributions **YY** and **YR** written the manuscript, and carried out the data analysis. **YSZ** and **CCG** collected and cleaned the data. **YG** and **JXS** participated in the revision of the manuscript. **RC** and **SFL** conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials The dataset used during this study is available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate The ethics committee of the Children's Hospital of Nanjing Medical University approved this study (No. NJCH202004037-1). The institutional review board committee exempted the study from informed consent because of its retrospective nature. All data were anonymized before further statistical analysis. All the procedures were followed according to the Declaration of Helsinki.

Consent for publication All authors listed have read the complete manuscript and approved the paper's submission.

Conflict of interest The authors declare no competing interests.

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