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Epidemiology of Neonatal Acute Respiratory Distress Syndrome: Prospective, Multicenter, International Cohort Study

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OBJECTIVES: Age-specific definitions for acute respiratory distress syndrome (ARDS) are available, including a specific definition for neonates (the "Montreux definition"). The epidemiology of neonatal ARDS is unknown. The objective of this study was to describe the epidemiology, clinical course, treatment, and outcomes of neonatal ARDS.

DESIGN: Prospective, international, observational, cohort study.

SETTING: Fifteen academic neonatal ICUs.

PATIENTS: Consecutive sample of neonates of any gestational age admitted to participating sites who met the neonatal ARDS Montreux definition criteria.

MEASUREMENTS AND MAIN RESULTS: Neonatal ARDS was classified as direct or indirect, infectious or noninfectious, and perinatal (≤ 72 hr after birth) or late in onset. Primary outcomes were: 1) survival at 30 days from diagnosis, 2) inhospital survival, and 3) extracorporeal membrane oxygenation (ECMO)-free survival at 30 days from diagnosis. Secondary outcomes included respiratory complications and common neonatal extrapulmonary morbidities. A total of 239 neonates met criteria for the diagnosis of neonatal ARDS. The median prevalence was 1.5% of neonatal ICU admissions with male/female ratio of 1.5. Respiratory treatments were similar across gestational ages. Direct neonatal ARDS (51.5% of neonates) was more common in term neonates and the perinatal period. Indirect neonatal ARDS was often triggered by an infection and was more common in preterm neonates. Thirty-day, inhospital, and 30-day ECMO-free survival were 83.3%, 76.2%, and 79.5%, respectively. Direct neonatal ARDS was associated with better survival outcomes than indirect neonatal ARDS. Direct and noninfectious neonatal ARDS were associated with the poorest respiratory outcomes at 36 and 40 weeks' postmenstrual age. Gestational age was not associated with any primary outcome on multivariate analyses.

CONCLUSIONS: Prevalence and survival of neonatal ARDS are similar to those of pediatric ARDS. The neonatal ARDS subtypes used in the current definition may be associated with distinct clinical outcomes and a different distribution for term and preterm neonates.

KEY WORDS: acute respiratory distress syndrome; neonatal intensive care unit; neonate; outcome; respiratory failure

Acute respiratory distress syndrome (ARDS) was first described in 1967 and remains a life-threatening condition (1, 2). ARDS may occur at any age, leading to the development of age-specific definitions for adult (3), pediatric (PARDS) (4), and neonatal (NARDS) (5) patients. The Montreux definition of NARDS was released for clinical and research purposes in 2017 as the first phase of the Neonatal ARDS Project (5). This consensus definition

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RESEARCH IN CONTEXT

- Age-specific acute respiratory distress syndrome (ARDS) diagnostic criteria for adults and children have allowed the development of evidence-based therapies.
- Diagnostic criteria for neonatal ARDS (NARDS) were proposed in 2017 (the "Montreux" definition).
- The Montreux definition for NARDS is untested in clinical practice and the epidemiology, treatments, and outcomes are unknown.

acknowledges the many pathobiological and pathophysiological features of ARDS shared across all age groups, while it identifies features in neonates that are distinct from older populations (6–9). Specifically, the Montreux definition of NARDS considers the unique neonatal lung biology and structure; reduced local and systemic immune defenses; the pathophysiological differences compared with primary surfactant deficiency (respiratory distress syndrome [RDS]); the unpredictable physiologic effects of transition from fetal life; and different approaches to respiratory therapies compared with older populations (5, 10). Highlighting these differences is needed, as some common ARDS triggers are different in neonates, such as sepsis, which has unique immunological and pathophysiological features in neonates and does not have yet a dedicated diagnostic score.

The objective of the second phase of the Neonatal ARDS Project was to perform a prospective study aiming to: 1) determine the prevalence of NARDS using the Montreux definition and 2) describe the epidemiology, clinical course, treatment, and outcomes of neonates meeting the NARDS diagnostic criteria. These aims, and the applied methodology, are similar to the processes undertaken after the formulation of the Berlin definition of ARDS and the Pediatric Acute Lung Injury Consensus Collaborative definition for adults and children, respectively (3, 11).

METHODS

Study Design and Setting

A prospective, multicenter, international, observational, cohort study was conducted in neonatal ICUs (NICUs) under the supervision of the Neonatal ARDS Project steering committee. The study was approved by each local ethical board or used the coordinating center approval (French Critical Care Ethical Commission; n.SRLF-15-05). Parental/guardian consent was obtained if required by local regulations. Composition of the steering committee and detailed study methods are provided in the **Online Supplement** (http://links.lww.com/PCC/C49).

Patients

All inpatients were screened daily in each center. Both inborn and outborn neonates were considered for inclusion. Neonates were consecutively enrolled when deemed eligible for inclusion if they fulfilled all the Montreux definition criteria in the previous 24 hours, without any exclusion criteria (5). Briefly, neonates were excluded if they had: 1) RDS due to primary surfactant deficiency (such as hyaline membrane disease), transient tachypnoea of the neonate or congenital lung malformations; 2) congenital heart disease-causing pulmonary edema; and 3) known genetic syndromes or chromosomopathies. Neonates were also excluded during analysis if: 1) outcome data were unavailable; 2) data were inconsistent with the Montreux definition criteria (5); or 3) oxygenation was evaluated with venous blood gas analysis.

Data Collection

Data were prospectively collected for patients until hospital discharge or death, using an anonymized web-based database in research electronic data capture (12). The total number of admissions to each NICU were recorded to calculate the prevalence of NARDS. Due to the noninterventional study design, the timing of blood gas analysis could not be standardized across participating centers and was only recorded at NARDS diagnosis. Blood gas analysis is also performed less frequently in NICU compared with adult and pediatric critical care. Arterial access is also less common, necessitating the use of transcutaneous measures or arterialized capillary blood sampling (when appropriate). The Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II) was calculated (13). Respiratory support variables were recorded at NARDS diagnosis and at highest clinical severity. The steering committee unanimously agreed to allow the

definition of highest clinical severity time-point to be determined by local attending physicians, considering all available relevant data, rather than a single prespecified parameter.

Each NARDS event was classified as: 1) direct or indirect, 2) infectious or noninfectious, 3) according to timing of onset, and 4) illness severity. The classification of direct and indirect NARDS was based on the concept of pulmonary (primary) or extrapulmonary (secondary) origin of triggers, respectively, consistent with approaches for PARDS and ARDS (14, 15). Direct NARDS was defined as resulting from the following pulmonary triggers: aspiration, bronchiolitis, lung hemorrhage, pertussis, and/or pneumonia. Indirect NARDS resulted from extrapulmonary triggers including perinatal asphyxia, chorioamnionitis, gastrointestinal perforation, necrotizing enterocolitis (NEC), sepsis, and surgery. Infectious NARDS was triggered by bronchiolitis, pertussis, pneumonia, chorioamnionitis, and sepsis. Timing of NARDS onset was defined as perinatal (≤ 72 hr of birth) or late (> 72 hr after birth). Finally, NARDS severity was classified as mild, moderate, or severe based on the oxygenation index (OI) at NARDS diagnosis (OI 4–7.9, 8–15.9, or ≥ 16, respectively) (5). In noninvasively ventilated patients, OI was calculated using the mean airway pressure (Paw) and Pao_2 (arterial or transcutaneous) measured when airway leak was minimized (appropriately sized interfaces, chinstrap, and/or actively closing the mouth) (5). Multiple triggers were allowed and neonates could be assigned to multiple types of NARDS. Consistent with the approach used for PARDS, the classification was finalized after discussion between the Steering Committee and local investigators following review of medical records (14).

Outcomes

The primary outcomes were: 1) survival at 30 days from NARDS diagnosis, 2) inhospital survival, and 3) extracorporeal membrane oxygenation (ECMO)-free survival at 30 days from NARDS diagnosis. Mortality is an objective and clinically relevant outcome that mirrors comparative studies of ARDS and PARDS (14, 16). The choice of these outcomes allows the comparison of the consequences of ARDS in infants of different age and gives a comprehensive description of mortality. Secondary outcomes included respiratory complications, common neonatal extrapulmonary morbidities and respiratory status at 36 and 40 weeks postmenstrual age for those neonates born less than or equal to 32 weeks' gestation.

Sample Size and Statistical Analysis

As this is the first study on a newly defined condition, a convenience sample of 220 neonates meeting the NARDS criteria was used. This was similar to that used to study the Berlin definition in children (6).

Data were compared per types of NARDS and gestational age classes with Fisher exact and Wilcoxon signed-rank tests, or Student *t* test and one-way analysis of variance (with Sidak post hoc test), as appropriate. Primary outcomes were displayed with Kaplan-Meier curves and compared with the Breslow test for the different types of NARDS (direct/indirect, infectious/noninfectious, mild/moderate/severe). The timing (perinatal/late) of NARDS onset was not included in these analyses due to the near identical distribution of demographic and clinical characteristics between direct/indirect and perinatal/late onset NARDS.

Primary and secondary outcomes were analyzed with Cox proportional and logistic regressions, respectively, using a backward-stepwise method (covariates were removed from the model if significance was $p > 0.10$). The choice of covariates was discussed and decided by unanimous agreement within the steering committee, based on their epidemiological role and biological relevance, demographic and clinical characteristics, and previously reported association with outcomes (6, 11, 13-15, 17-24). The following covariates were chosen: gestational age, type of NARDS (direct/indirect), severity class, NARDS trigger (infectious/noninfectious), recruiting center, sex, SNAPPE-II score, and postnatal age at NARDS diagnosis. Oxygen dependency and need for respiratory support at 36 and 40 weeks' postmenstrual age were analyzed only for neonates less than or equal to 32 weeks' gestation. Multivariable analyses of secondary outcomes were performed both on the whole population and on survivors. There was no correction for multiple comparisons in univariate analyses. Analyses were performed with SPSS 15 (SPSS, Chicago, IL), MedCalc 13 (MedCalc, Ostend, Belgium), and Stata 15 (StataCorp, College Station, TX).

RESULTS

Epidemiology

Two hundred thirty-nine neonates from 15 NICUs (Australia, Brazil, China, Finland, France, Israel,

Italy, The Netherlands, Switzerland, and United States) met the criteria for NARDS, had correct and complete data entered, and were included in the final analysis: 24 neonates were excluded because they did not meet the Montreux definition or had incomplete outcome data (**eFig. 1**, http://links.lww.com/PCC/C49). During the study period, 15,916 neonates were admitted to these NICUs, resulting in a NARDS prevalence of 1.5% overall. This varied among participating centers from 1% to 5%. **Table 1** describes the characteristics of included neonates: 92 (34.3%) neonates were extremely preterm (23–28 wk gestation), 34 (13.4%) preterm (29–33 wk), 19 (7.9%) late preterm (34–36 wk), and 94 (39.3%) term (> 36 wk). **eTable 1** (http://links.lww.com/PCC/C49) describes the characteristics of the infants born less than or equal to 32 weeks with perinatal onset. There was a preponderance of male neonates (60.7%). 51.5%, 57.7%, and 54.4% of neonates presented with direct, infectious, or perinatal NARDS, respectively. Age and OI at the diagnosis were widely distributed. NARDS were severe in 55.6%, moderate in 28.9%, and mild in 15.5% of neonates. The most common comorbidities were patent ductus arteriosus (28%), acute renal failure (5%), jaundice (7.5%), coagulation (5.8%), and metabolic disorders (5.4%). The prevalence of pulmonary hypertension was more common in term (≥ 37 wk gestation; 23.4%) than in preterm neonates (≤ 28 wk: 8.7%; 29 and 32 wk: 6.5%; and between 33 and 36 wk: 18.5%; $p = 0.019$).

eFigure 2 (http://links.lww.com/PCC/C49) shows the cumulative NARDS prevalences from birth until hospital discharge or death by gestational age and NARDS type. Overall, NARDS occurred earlier in postnatal life for term neonates and for direct or noninfectious NARDS. The cumulative prevalence was similar across NARDS severity. Sepsis was the most common NARDS trigger, followed by aspiration (primarily meconium aspiration), with multiple triggers identified in 27.6% of neonates (**Table 2**). The distribution of triggers based upon clinical severity and gestational age is presented in **eTable 2** (http://links.lww.com/PCC/C49).

Respiratory Support and Additional Treatment

High-frequency oscillatory ventilation (HFOV) was the most common type of respiratory support (**eFig. 3**, http://links.lww.com/PCC/C49: 60% of patients at time of diagnosis and 69% at greatest disease severity; $p < 0.001$). ECMO was rarely used (4%). The median (25th–75th percentile) duration of ECMO was 140 hours (56–215 hr). The Paw was 14 cm H_2O (11–17 cm H_2O) at NARDS diagnosis and 17 cm H_2O (14–20 cm

TABLE 1.
Demographic and Clinical Characteristics of the Entire Population of Neonates Meeting the Neonatal Acute Respiratory Distress Syndrome Criteria

n = 239 Neonates	Summary Statistic	Minimum–Maximum
Female	94 (39.3%)	Not applicable
Gestational age (wk)	32.3 (6.4)	23–42
Birth weight (g)	2,046 (1,278)	475–5,220
Birth weight *z* score	−0.1 (1.1)	−8.8 to 3.5
5′ Apgar score	7 (6–9)	0–10
Score for Neonatal Acute Physiology with Perinatal Extension-II score	34 (20.4)	0–81
Postnatal age at NARDS diagnosis (d)	2 (0–15)	0–126
Weight at NARDS diagnosis (g)	2,163 (1,267)	435–5,650
Oxygenation index at NARDS diagnosis	17.7 (10.7–29.5)	4–185
NICU stay (d)	24 (10–68)	2–221
NICU stay after NARDS diagnosis (d)	16 (8–50)	1–189

NARDS = neonatal acute respiratory distress syndrome, NICU = neonatal ICU.
The summary statistic is expressed for the whole cohort ($n = 239$) as number (%) for female and otherwise as mean (SD) or median (25th–75th percentiles). Additionally, minimum–maximum values are shown. Apgar and Score for Neonatal Acute Physiology with Perinatal Extension-II are dimensionless scores.

AT THE BEDSIDE

- The prevalence and survival of NARDS were similar to those of pediatric ARDS. NARDS patients are generally severely ill and require high-acuity therapies.
- Direct NARDS was associated with term neonates, perinatal onset and had a lower mortality than indirect NARDS. Indirect NARDS was associated with an infectious trigger and was more common in neonates born preterm.
- The Montreux definition of NARDS is appropriate to diagnose ARDS in neonates and describe the epidemiology of NARDS.

H_2O) at the time of greatest disease severity for invasively ventilated neonates ($p < 0.0001$). During conventional ventilation, expiratory tidal volume was also higher at greatest disease severity (6.1 mL/kg [5.0–8.0 mL/kg]) than at onset (5.3 mL/kg [4.6–6.3 mL/kg]; $p = 0.001$). Total duration of oxygen supplementation, noninvasive respiratory support (any type), and invasive ventilation were 13 days (5–48 d), 7 days (1–34 d), and 7 days (4–14 d), respectively. NARDS was treated with at least one bolus of surfactant in 57.7% neonates, while 10.9% of neonates received surfactant diluted via bronchoalveolar lavage because of direct, noninfectious NARDS. **eTable 3** (http://links.lww.com/PCC/C49) describes respiratory therapies by NARDS classification: Paw was higher and surfactant use more frequent in direct and noninfectious NARDS; Paw was higher and HFOV was more often used in patients with severe NARDS.

Primary Outcomes

Thirty-day, inhospital, and 30-day ECMO-free survival were 83.3%, 76.2%, and 79.5%, respectively. The 30-day and inhospital survival were higher for direct than indirect NARDS (**Figs. 1** and **2**). Thirty-day ECMO-free survival was higher for infectious than noninfectious NARDS ($p = 0.03$) and decreased with worsening NARDS severity (**eFig. 4**, http://links.lww.com/PCC/C49). Direct NARDS was associated with higher 30 days, inhospital, and 30-day ECMO-free survival on multivariable analysis (**Table 3**).

Secondary Outcomes and Respiratory Complications

Multivariable regression models adjusted for confounders identified direct and infectious NARDS being associated with greater oxygen dependency and need for respiratory support at 36 weeks' postmenstrual age (**eTable 4**, http://links.lww.com/PCC/C49). Infectious NARDS was similarly associated with a greater need for respiratory support at 40 weeks' postmenstrual age. There was no effect of NARDS type on other outcomes. Respiratory treatments, primary, and main secondary outcomes by gestational age are shown in **eTable 5** (http://links.lww.com/PCC/C49). All mortality outcomes increased with increasing prematurity on univariate but not multivariate analysis.

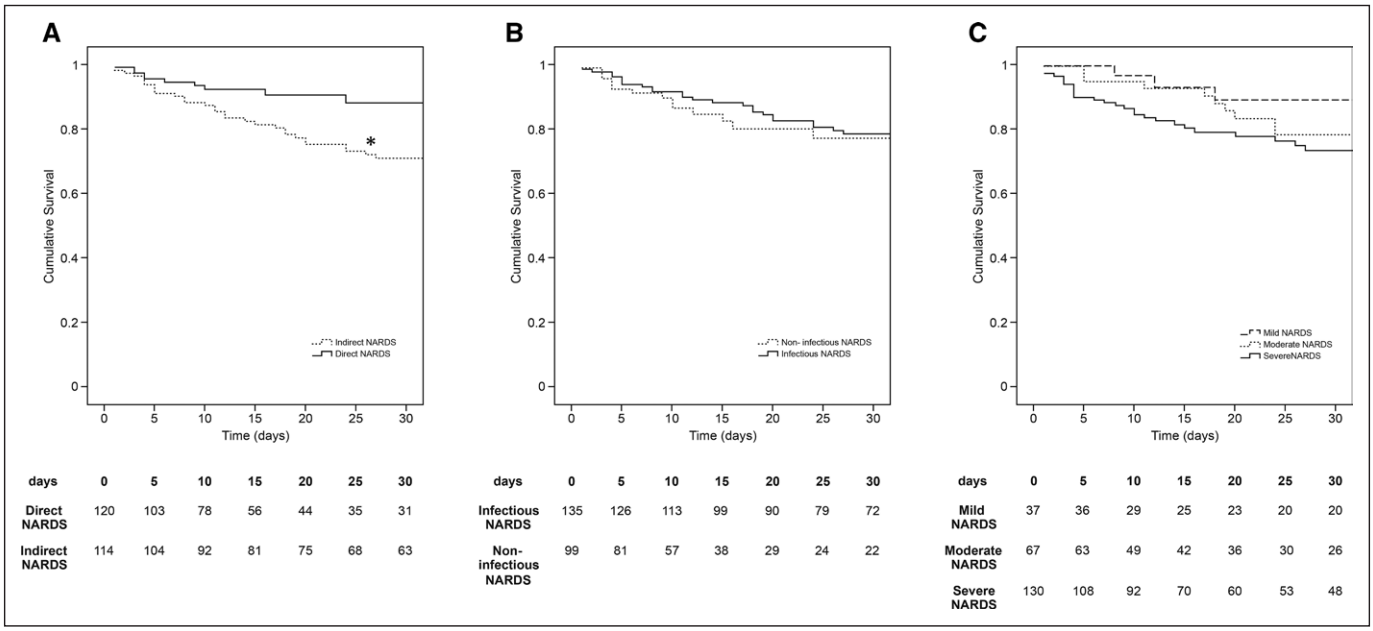
DISCUSSION

To the best of our knowledge, this is the first epidemiological description of ARDS in a neonatal population. Neonates have not benefited from the recent adult and PARDS definitions due to limited translatability of the ARDS diagnostic criteria to the perinatal period (10). We found that ARDS may develop in this age group,

TABLE 2.
Neonatal Acute Respiratory Distress Syndrome Triggers

Triggers	*n* (%)
Sepsis	90 (37.7)
Aspiration	65 (27.2)
Pneumonia	38 (15.9)
Lung hemorrhage	25 (10.5)
Necrotizing enterocolitis	23 (9.6)
Chorioamnionitis	8 (3.3)
Perinatal asphyxia	7 (2.9)
Postsurgical	6 (2.5)
Bronchiolitis	3 (1.3)
Gastrointestinal single perforation	2 (0.8)
Pertussis	2 (0.8)
Cardiorespiratory arrest	2 (0.8)
Biliary pneumonia	1 (0.4)

Triggers are listed in order of frequency. Multiple triggers were possible. Aspirations were represented by meconium (61 [25.5%], blood [5 (2.1%]) and milk (3 [1.3%]) aspirations, respectively.

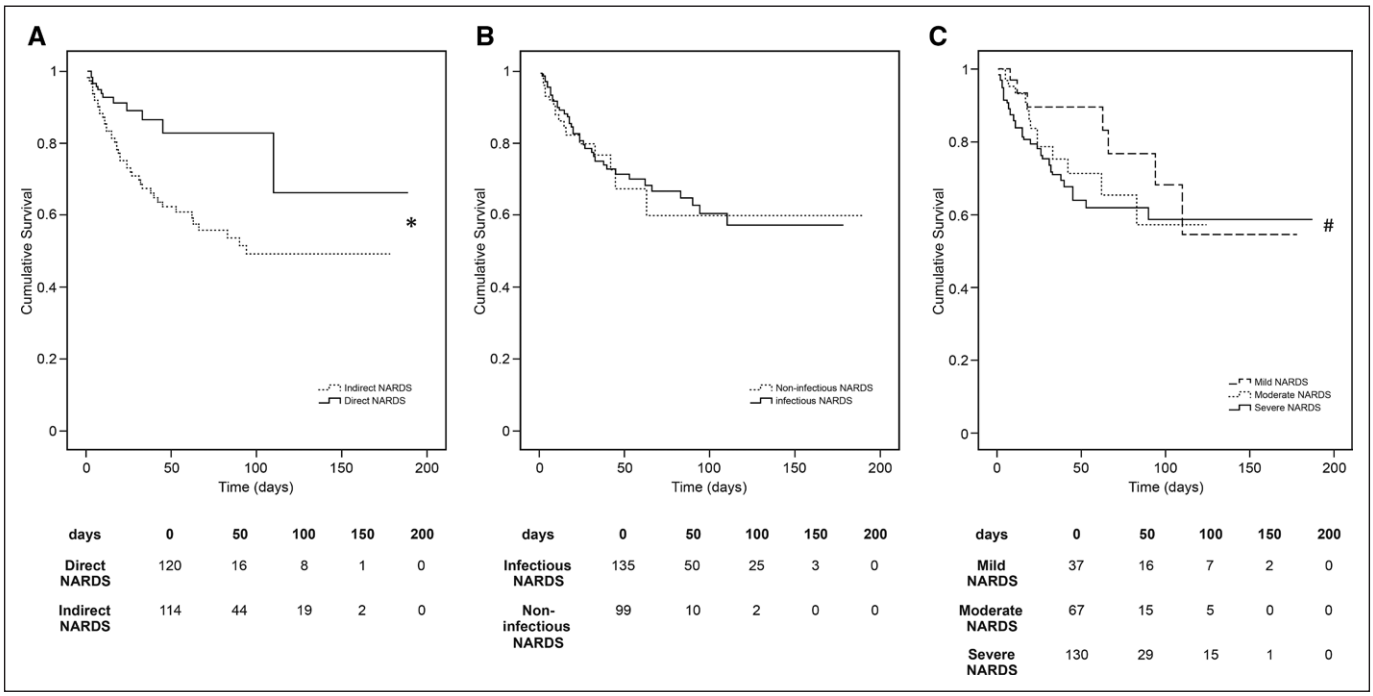


days	0	5	10	15	20	25	30
Direct NARDS	120	103	78	56	44	35	31
Indirect NARDS	114	104	92	81	75	68	63

days	0	5	10	15	20	25	30
Infectious NARDS	135	126	113	99	90	79	72
Non-infectious NARDS	99	81	57	38	29	24	22

days	0	5	10	15	20	25	30
Mild NARDS	37	36	29	25	23	20	20
Moderate NARDS	67	63	49	42	36	30	26
Severe NARDS	130	108	92	70	60	53	48

Figure 1. Kaplan-Meier analyses for 30-d survival. Direct and indirect, infectious and noninfectious, and mild, moderate, and severe neonatal acute respiratory distress syndrome (NARDS) are shown in **A–C**, respectively. *$p = 0.02$, direct versus indirect NARDS; $p = 0.505$, infectious versus noninfectious NARDS; $p = 0.06$, between NARDS severity classes (Breslow test). Number of neonates at each time point are shown in tables below the curves. The timing (perinatal/late) of NARDS onset was not included in these analyses since the distribution of basic demographic and clinical characteristics was identical between direct/indirect and perinatal/late onset subtypes of NARDS.



days	0	50	100	150	200
Direct NARDS	120	16	8	1	0
Indirect NARDS	114	44	19	2	0

days	0	50	100	150	200
Infectious NARDS	135	50	25	3	0
Non-infectious NARDS	99	10	2	0	0

days	0	50	100	150	200
Mild NARDS	37	16	7	2	0
Moderate NARDS	67	15	5	0	0
Severe NARDS	130	29	15	1	0

Figure 2. Kaplan-Meier analyses for inhospital survival. Direct and indirect, infectious and noninfectious, and mild, moderate, and severe neonatal acute respiratory distress syndrome (NARDS) are shown in **A–C**, respectively. *$p = 0.011$, direct versus indirect NARDS; $p = 0.429$, infectious versus noninfectious NARDS; #$p = 0.04$, between NARDS severity classes (Breslow test). Number of neonates at each time point are shown in tables below the curves. The timing (perinatal/late) of NARDS onset was not included in these analyses since the distribution of basic demographic and clinical characteristics was identical between direct/indirect and perinatal/late onset subtypes of NARDS.

TABLE 3.
Multivariable Analysis for Co-Primary Outcomes

Outcome	Adjusted Hazard Ratio (95% CI)	*p*
30-d survival		
Male sex	2.9 (1.3–6.4)	0.007
Postnatal age at NARDS diagnosis (d)	0.88 (0.82–0.94)	< 0.0001
Type of NARDS (direct vs indirect)	0.15 (0.05–0.45)	0.001
Inhospital survival		
Male sex	1.9 (1.0–3.6)	0.03
Postnatal age at NARDS diagnosis (d)	0.97 (0.96–0.99)	0.04
Type of NARDS (direct vs indirect)	0.23 (0.10–0.52)	< 0.0001
30-d extracorporeal membrane oxygenation-free survival		
Postnatal age at NARDS diagnosis (d)	0.91 (0.87–0.96)	< 0.0001
Type of NARDS (direct vs indirect)	0.28 (0.12–0.68)	0.005

NARDS = neonatal acute respiratory distress syndrome.
Thirty-d mortality, the composite endpoint of 30-d mortality and/or need for extracorporeal membrane oxygenation, and the inhospital mortality were adjusted for gestational age, type of NARDS (direct/indirect), severity class, NARDS trigger (infectious/noninfectious), recruiting center, sex, Score for Neonatal Acute Physiology with Perinatal Extension-II score, and postnatal age at NARDS diagnosis (in d from birth) using Cox proportional regression models. Results are presented as adjusted hazard ratio and 95% CI. Only covariates significantly associated with the outcomes and remaining at the last regression step are shown. Analysis was performed for the whole cohort ($n = 239$). The timing (perinatal/late) of NARDS onset was not included in these analyses since the distribution of basic demographic and clinical characteristics was identical between direct/indirect and perinatal/late onset subtypes of NARDS.

and across different developmental lung state, suggesting that NARDS can be reasonably classified using the ARDS types already identified in adults and children. However, although NARDS shares common features with PARDS, it has relevant differences in the trigger profile and treatment.

In our population, the overall prevalence of NARDS was 1.5% of NICU admissions (ranging from 1% to 5% between participating units), similar to the 1%–4% of PICU admissions reported for PARDS (11, 23, 25, 26). The overall mortality for NARDS was 17%–24%, similar to the 17%–33% reported in recent PARDS studies (11, 27), but much higher than mortality for the general NICU population (3%–9% in developed countries) (28). Both 30-day and 30-day ECMO-free survival overtime were similar to reports of PARDS in older children (6). Conversely, the mortality was lower than reported in adult ARDS (3). This may be explained by the different trigger profile and relative absence of severe chronic comorbidities in neonates and children (29). Some biological factors unique to neonates may also play a role: the neonatal lung is less capable of producing inflammation and fibrosis and has a relatively higher amount of surfactant in a smaller volume compared with the adult lung (22). Conversely, the inflammatory response in preterm and term neonates is not the same, with preterm neonates being more sensitive to impaired alveolarization and lung injury from a persistent proinflammatory state.

In adults and children, direct (pulmonary) and indirect (extrapulmonary) ARDS have a different clinical course and pathophysiology, with predominantly epithelial injury for direct and endothelial injury for indirect ARDS (15, 19). In these groups, there are greater oxygen impairment and higher lung injury scores for direct ARDS, while indirect ARDS has a greater likelihood of multiple organ failure (14, 30). Interestingly, these differences do not translate to differences in mortality (20, 21). Conversely, we found differences in the triggers and mortality of direct and indirect NARDS with a higher mortality in the latter. This is likely explained by the association between later-onset and prematurity-associated comorbidities in the indirect NARDS group (31).

Previous definitions of PARDS excluded the onset of ARDS within the perinatal period and preterm neonates. This provides a rationale for the need to develop a NARDS definition, and we found that both are

important components of the NARDS population (5). The distinction between perinatal (≤ 72 hr) and late onset (> 72 hr after birth) is important given the spectrum of perinatal events that can trigger NARDS. For instance, the frequent occurrence of birth-related aspiration in term neonates explains the high prevalence we observed in noninfectious, direct NARDS. Conversely, preterm neonates typically require prolonged NICU care with late complications, such as sepsis and NEC, that are associated with indirect, infectious, and late-onset NARDS. Similar to PARDS, our data confirm that sepsis was a common trigger for NARDS (11, 14). An infectious cause of NARDS did not influence mortality but was associated with oxygen dependency and/or need for respiratory support at 36 and 40 weeks' postmenstrual age. Persistence of NARDS-induced cellular damage, eventually perpetuated by aggressive ventilation, similar to ventilator-associated pneumonia could contribute to chronic lung disease development especially in preterm neonates (32). Long-term respiratory status is a multifactorial and complex outcome, and future studies will have to be performed to clarify which role NARDS plays in it.

ARDS severity discriminates mortality in adults and children (3, 6, 11). We did not find a significant relationship between mortality and NARDS severity using an OI-based classification. However, our study was not designed to specifically address the use of NARDS severity classification to predict mortality. Some infants had relatively low OI, but the majority met the definition for moderate or severe NARDS. As explained in the Online Supplement (http://links.lww.com/PCC/C49), this finding is likely related to participation in the study of primarily large academic units, with the potential for a bias toward sicker infants. As such, this bias may affect the validity of mild NARDS diagnosis, also because cases with lower oxygenation impairment might be due to neonatal lung disorders other than NARDS, whose exclusion may partially depend on the clinical expertise. It was also impossible to standardize blood gas analysis, hampering the use, and reliability of severity grading. Noninvasive ventilation and the use of uncuffed endotracheal tubes are the norm in neonates, limiting the reliability of Paw assessment compared with older populations. Therefore, in some infants, OI should be considered as an estimation when arterial blood gas or accurate Paw values are unavailable. The Montreux definition provides guidance on how to obtain the most accurate calculation and mandates a hierarchical approach to considering OI validity (5). Future studies should also record the method of oxygen and Paw assessment and consider the applicability of proxy measures of OI such as peripheral oxygen saturation/F_{IO_2} that are often easier to calculate in the NICU. Notwithstanding these issues, there is a sound pathophysiological and practical rationale to use oxygenation deficit as a core component of any ARDS definition, and OI as has been previously applied for PARDS (33). Our data will inform properly powered evaluation of OI-based NARDS severity grades and their predictive ability.

Unlike for PARDS and ARDS, HFOV was the most common mode of respiratory support at NARDS diagnosis. Exogenous surfactant was also used in the majority of cases, whilst ECMO was rarely used (3, 6, 11). Surfactant and HFOV are well-established rescue therapies for severe respiratory failure in neonates, especially for conditions associated with direct and noninfectious NARDS (34, 35). Direct ARDS is more likely to result in surfactant dysfunction and alveolar derecruitment (14, 30, 36, 37). There were no significant differences in treatments across gestation, and this reinforces the independency of NARDS concept from patients' age. ECMO is generally reserved as rescue for respiratory failure in term neonates not responding to HFOV and is used infrequently for sepsis (38). ECMO is also more commonly used in term or postterm neonates. The rare use of ECMO could be partially due to the relatively low number of term/late preterm neonates and the varying availability of this technique in participating sites. Our findings suggest that the applied treatments are similar for the majority of patients. This indicates that a NARDS classification provides a framework that can be used in future studies of novel ARDS therapies and outcomes, as recently suggested for surfactant (39).

We acknowledge some limitations, and these are discussed in more depth in the Online Supplement (http://links.lww.com/PCC/C49). NARDS and RDS following primary surfactant deficiency may coexist. However, the Montreux definition provides criteria to differentiate the two and identify the predominant cause of respiratory failure (5). It is interesting to note that use of invasive ventilation was higher in NARDS (eFig. 3, http://links.lww.com/PCC/C49) than reported for RDS (39). Our observational study was intentionally pragmatic as the introduction of the NARDS definition is novel in NICU care. We avoided an explanatory design, which is more suitable to investigating particular

patient subgroups or settings in previously well-understood topics (40, 41). For this reason, we decided to not include a comparative control group. Future studies of NARDS should focus on enrolling specific NARDS and control subgroups. Such an approach would allow exploration of potential contributing factors for NARDS, particularly associations between gestation, lung development, maternal factors, and NARDS onset or course. The use of standardized definitions and data review mitigate some limitations of our design. For example, chest imaging was not reviewed centrally, but local investigators were provided with radiological datasets to guide assessment (6). Allowing the highest clinical severity to be defined by clinicians using broad criteria may be a source of bias. Conversely, the use of specific a priori criteria (such as OI or Paw) may also introduce bias when the temporal trajectory of the disease, the treatment patterns and the validity of criteria to describe the disease are unknown, or measurements cannot be fully standardized. A formal power calculation was impossible because this was the first study on a newly defined condition. The potential for underpower cannot be discounted, although sample size was robust and comparable to sample sizes used to evaluate PARDS definitions (5, 6). The limited number of patients treated with ECMO might also have hindered the evaluation of ECMO-free survival as primary outcome. We cannot exclude that the lack of familiarity with this newly defined medical condition might have led to an underestimation of NARDS prevalence. The association between direct NARDS and oxygen dependency at 36 weeks might be partially due to more neonates with direct NARDS reaching the secondary endpoint. Finally, we choose extrapulmonary outcomes that are commonly used in NICUs, but these are also associated with multifactorial complications of prematurity. Thus, it is not surprising that none of these extrapulmonary outcomes were associated with any specific NARDS type within the study population constraints.

CONCLUSIONS

The prevalence and survival of NARDS were similar to those of PARDS. NARDS patients are generally severely ill and require high acuity therapies. Direct NARDS was associated with term neonates, perinatal onset and had a lower mortality than indirect NARDS. Indirect NARDS was associated with an infectious trigger and was more common in preterm neonates. Overall, the Montreux definition is appropriate to diagnose NARDS and describe its epidemiology.

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Neonatal ARDS Project Collaboration Group Members are listed in the ***Appendix****.*

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Drs. De Luca and Tingay were involved in study conception and design, data acquisition and interpretation, article drafting, and administrative, technical, or material support. Dr. van Kaam was involved in study design, data acquisition and interpretation, and article revision for important intellectual content. Dr. Courtney was involved in study design, data acquisition and interpretation, and article revision for important intellectual content. Dr. Kneyber was involved in study design, data interpretation, and article revision for important intellectual content. Dr. Tissieres was involved in study design, data acquisition and interpretation, and article revision for important intellectual content, administrative, technical, or material support equivalent to funding. Dr. Tridente was involved in data analysis and interpretation, article drafting, and technical support. Dr. Rimensberger was involved in study conception and design, data acquisition and interpretation, article revision for important intellectual content, and general supervision. Dr. Pillow was involved in study conception, design and supervision, design of database and provision of informatic tools, data interpretation, article revision for important intellectual content, and technical support. All authors approved the final article version to be published and agree to be accountable for all aspects of the work.

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REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
2. McNicholas BA, Rooney GM, Laffey JG: Lessons to learn from epidemiologic studies in ARDS. *Curr Opin Crit Care* 2018; 24:41–48
3. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
4. Khemani RG, Smith LS, Zimmerman JJ, et al; Pediatric Acute Lung Injury Consensus Conference Group: Pediatric acute respiratory distress syndrome: Definition, incidence, and epidemiology: Proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015; 16:S23–S40
5. De Luca D, van Kaam AH, Tingay DG, et al: The Montreux definition of neonatal ARDS: Biological and clinical background behind the description of a new entity. *Lancet Respir Med* 2017; 5:657–666
6. De Luca D, Piastra M, Chidini G, et al; Respiratory Section of the European Society for Pediatric Neonatal Intensive Care (ESPNIC): The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: Multicenter evaluation and expert consensus. *Intensive Care Med* 2013; 39:2083–2091
7. Wong JJ, Phan HP, Phumeetham S, et al; Pediatric Acute & Critical Care Medicine Asian Network (PACCMAN): Risk stratification in pediatric acute respiratory distress syndrome: A multicenter observational study. *Crit Care Med* 2017; 45:1820–1828
8. Khemani RG, Rubin S, Belani S, et al: Pulse oximetry vs. PaO_2 metrics in mechanically ventilated children: Berlin definition of ARDS and mortality risk. *Intensive Care Med* 2015; 41:94–102
9. Randolph AG: Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med* 2009; 37:2448–2454
10. De Luca D: Personalising care of acute respiratory distress syndrome according to patients' age. *Lancet Respir Med* 2019; 7:100–101
11. Khemani RG, Smith L, Lopez-Fernandez YM, et al; Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) Investigators; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): An international, observational study. *Lancet Respir Med* 2019; 7:115–128
12. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–381
13. Richardson DK, Corcoran JD, Escobar GJ, et al: SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J Pediatr* 2001; 138:92–100
14. Yehya N, Keim G, Thomas NJ: Subtypes of pediatric acute respiratory distress syndrome have different predictors of mortality. *Intensive Care Med* 2018; 44:1230–1239

15. Sinha P, Calfee CS: Phenotypes in acute respiratory distress syndrome: Moving towards precision medicine. *Curr Opin Crit Care* 2019; 25:12–20
16. Laffey JG, Kavanagh BP: Fifty years of research in ARDS. Insight into acute respiratory distress syndrome. From models to patients. *Am J Respir Crit Care Med* 2017; 196:18–28
17. Boghossian NS, Geraci M, Edwards EM, et al: Sex differences in mortality and morbidity of infants born at less than 30 weeks' gestation. *Pediatrics* 2018; 142:e20182352
18. Barros FC, Rossello JL, Matijasevich A, et al: Gestational age at birth and morbidity, mortality, and growth in the first 4 years of life: Findings from three birth cohorts in Southern Brazil. *BMC Pediatr* 2012; 12:169
19. Calfee CS, Janz DR, Bernard GR, et al: Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. *Chest* 2015; 147:1539–1548
20. Cochi SE, Kempker JA, Annangi S, et al: Mortality trends of acute respiratory distress syndrome in the United States from 1999 to 2013. *Ann Am Thorac Soc* 2016; 13:1742–1751
21. Killien EY, Mills B, Vavilala MS, et al: Association between age and acute respiratory distress syndrome development and mortality following trauma. *J Trauma Acute Care Surg* 2019; 86:844–852
22. Kneyber MC, Zhang H, Slutsky AS: Ventilator-induced lung injury. Similarity and differences between children and adults. *Am J Respir Crit Care Med* 2014; 190:258–265
23. Yu WL, Lu ZJ, Wang Y, et al; Collaborative Study Group of Pediatric Respiratory Failure: The epidemiology of acute respiratory distress syndrome in pediatric intensive care units in China. *Intensive Care Med* 2009; 35:136–143
24. Shim SY, Cho SJ, Kong KA, et al: Gestational age-specific sex difference in mortality and morbidities of preterm infants: A nationwide study. *Sci Rep* 2017; 7:6161
25. López-Fernández Y, Azagra AM, de la Oliva P, et al; Pediatric Acute Lung Injury Epidemiology and Natural History (PED-ALIEN) Network: Pediatric Acute Lung Injury Epidemiology and Natural History study: Incidence and outcome of the acute respiratory distress syndrome in children. *Crit Care Med* 2012; 40:3238–3245
26. Beltramo F, Khemani RG: Definition and global epidemiology of pediatric acute respiratory distress syndrome. *Ann Transl Med* 2019; 7:502
27. Wong JJ, Jit M, Sultana R, et al: Mortality in pediatric acute respiratory distress syndrome: A systematic review and meta-analysis. *J Intensive Care Med* 2019; 34:563–571
28. Chow S, Chow R, Popovic M, et al: A selected review of the mortality rates of neonatal intensive care units. *Front Public Health* 2015; 3:225
29. Matthay MA, Zemans RL, Zimmerman GA, et al: Acute respiratory distress syndrome. *Nat Rev Dis Primers* 2019; 5:18
30. Luo L, Shaver CM, Zhao Z, et al: Clinical predictors of hospital mortality differ between direct and indirect ARDS. *Chest* 2017; 151:755–763
31. Tissières P, Ochoda A, Dunn-Siegrist I, et al: Innate immune deficiency of extremely premature neonates can be reversed by interferon-γ. *PLoS One* 2012; 7:e32863
32. Dell'Orto V, Raschetti R, Centorrino R, et al: Short- and long-term respiratory outcomes in neonates with ventilator-associated pneumonia. *Pediatr Pulmonol* 2019; 54:1982–1988
33. Parvathaneni K, Belani S, Leung D, et al: Evaluating the performance of the pediatric acute lung injury consensus conference definition of acute respiratory distress syndrome. *Pediatr Crit Care Med* 2017; 18:17–25
34. Tingay DG, Mills JF, Morley CJ, et al: Indicators of optimal lung volume during high-frequency oscillatory ventilation in infants. *Crit Care Med* 2013; 41:237–244
35. Tingay DG, Mills JF, Morley CJ, et al: The deflation limb of the pressure-volume relationship in infants during high-frequency ventilation. *Am J Respir Crit Care Med* 2006; 173:414–420
36. Taut FJH, Rippin G, Schenk P, et al: A Search for subgroups of patients with ARDS who may benefit from surfactant replacement therapy: A pooled analysis of five studies with recombinant surfactant protein-C surfactant (Venticute). *Chest* 2008; 134:724–732
37. De Luca D, Piastra M, Tosi F, et al: Pharmacological therapies for pediatric and neonatal ALI/ARDS: An evidence-based review. *Curr Drug Targets* 2012; 13:906–916
38. Barbaro RP, Paden ML, Guner YS, et al; ELSO member centers: Pediatric extracorporeal life support organization registry international report 2016. *ASAIO J* 2017; 63:456–463
39. De Luca D, Cogo P, Kneyber MC, et al: Surfactant therapies for pediatric and neonatal ARDS: ESPNIC expert consensus opinion for future research steps. *Crit Care* 2021; 25:75
40. De Luca D, Harrison DA, Peters MJ: 'Lumping or splitting' in paediatric acute respiratory distress syndrome (PARDS). *Intensive Care Med* 2018; 44:1548–1550
41. Thorpe KE, Zwarenstein M, Oxman AD, et al: A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. *J Clin Epidemiol* 2009; 62:464–475

APPENDIX

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