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Antecedents of chronic lung disease following three patterns of early respiratory disease in preterm infants

Matthew Laughon, MD, MPH¹, Carl Bose, MD¹, Elizabeth N. Allred, MS^{2,3,4}, T. Michael O'Shea, MD, MPH⁵, Richard A. Ehrenkranz, MD⁶, Linda J. Van Marter, MD, MPH^{7,8,9}, Alan Leviton, MD, MS^{2,4}, and for the ELGAN Study Investigators

¹School of Medicine, Division of Neonatal-Perinatal Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC

²Harvard Medical School, Department of Neurology, Boston, MA

³Harvard School of Public Health, Department of Biostatistics, Boston, MA

⁴Children's Hospital, Department of Neurology, Boston MA

⁵Wake Forest University School of Medicine, Division of Neonatology, Winston-Salem, NC

⁶Yale University School of Medicine, Division of Perinatal Medicine, New Haven, CT

⁷Harvard Medical School, Department of Pediatrics, Boston, MA

⁸Children's Hospital, Division of Newborn Medicine, Boston, MA

⁹Brigham and Women's Hospital, Division of Newborn Medicine, Boston, MA

Abstract

OBJECTIVES/INTRODUCTION—The incidence of chronic lung disease (CLD) varies among groups defined by their early pattern of respiratory disease. Although CLD is common among infants with continuous exposure to increased ambient oxygen throughout the first two postnatal weeks the antecedents of CLD among preterm infants without this exposure are not well understood.

PATIENTS AND METHODS—We examined data collected prospectively on the 1204 (out of 1506) infants born in 2002 to 2004 at 23 to 27 completed weeks of gestation who survived to 36 weeks post-menstrual age (PMA). Based on their initial respiratory presentation and need for supplemental oxygen during the first two weeks, infants were classified as having early and persistent pulmonary dysfunction (EPPD), early recovery of pulmonary function followed by deterioration (PD), or consistently good pulmonary function characterized by low FiO₂ (Low FiO₂).

RESULTS—CLD was diagnosed in 69% of infants with EPPD, in 52% with PD, and 17% in the Low FiO₂ group. Risk factors for CLD varied among these groups. Birth weight z-score < -1

Address for Correspondence: ML, Division of Neonatal-Perinatal Medicine, UNC Hospital, CB#7596, Chapel Hill, NC 27599-7596, matt_laughon@med.unc.edu.

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conveyed information about CLD risk in all three groups and was the major risk factor for infants in the Low FiO₂ group (Odds Ratio [OR] 27; 95% confidence interval [CI] 7–95). Mechanical ventilation at 7 days was associated with increased risk in the pulmonary deterioration group (OR 4.2, 95% CI 2.5–6.9) and the early and persistent pulmonary dysfunction group (OR 2.7, 95% CI 1.5–4.7), but not the Low FiO₂ group (OR 1.5, 95% CI 0.5–3.9).

CONCLUSION—Both the likelihood of a very preterm infant developing CLD and the profile of risk factors linked with CLD are related to the infant’s pattern of respiratory disease during the first two postnatal weeks. Among infants with little exposure to oxygen during this period, fetal growth restriction, not mechanical ventilation, is the factor with the strongest association with CLD.

Keywords

lung disease; prematurity; preterm infant

OBJECTIVES/INTRODUCTION

Early pulmonary dysfunction in extremely low gestational age newborns (ELGANs) can be characterized by three distinct patterns, based on the fraction of inspired oxygen they require in the first two postnatal weeks.¹ A minority of ELGANs have relatively normal pulmonary function throughout the first two postnatal weeks. Another group has pulmonary deterioration (PD), characterized by resolving lung disease during the first postnatal week, and followed in the second week by a requirement for increased supplemental oxygen and, in some cases, mechanical ventilation. A third group has early and persistent pulmonary dysfunction (EPPD) requiring mechanical ventilation and high concentrations of supplemental oxygen throughout this time period.

The incidence of chronic lung disease (CLD), also known as bronchopulmonary dysplasia, varies among groups defined by their early respiratory function. Among infants with EPPD, approximately two-thirds develop CLD, and the oxygen and ventilation exposures in this group most resemble historical antecedents of BPD.¹ Infants with PD are at moderate risk of CLD and have less exposure to oxygen and ventilation than EPPD infants. Although almost one-fifth of infants with relatively normal lung function throughout the first two postnatal weeks develop CLD, they have virtually no exposure to supplemental oxygen and ventilation during that period. These observations suggest that several pathophysiologic pathways play a role in the development of CLD. Understanding the relative contribution of CLD antecedents within these groups might provide clues to the mechanisms of injury that lead to CLD.

The objective of this study was to identify clinical and demographic antecedents and modifiers of CLD risk in three groups of infants defined by their pattern of early postnatal respiratory function.

METHODS

The ELGAN Study

The infants included in this analysis are a subset of infants enrolled in a multi-center epidemiologic study to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs (the ELGAN Study).¹² From March 2002 to August 2004, women delivering before the 28th week of gestation at one of 14 participating institutions were asked to enroll in the study. Individual institutional review boards at each of the institutions approved the enrollment and consent processes (see Acknowledgements for the list of institutions that approved the study). Of 1506 infants enrolled, 1204 had both the information necessary to make an early respiratory status assignment and survived to 36 weeks post-menstrual age (PMA) when a CLD diagnosis was made.

Patterns of Early Respiratory Function and Chronic Lung Disease

ELGANs were classified into three mutually exclusive groups: those with relatively normal pulmonary function (Low FiO₂ group: FiO₂ consistently < 0.23 on all days between 3 and 7 postnatal days and receiving FiO₂ ≤ 0.25 on Day 14), those with pulmonary deterioration during the second week of life after a period of normal lung function (PD group: FiO₂ < 0.23 on any days between 3 and 7 days and receiving FiO₂ > 0.25 on day 14), and those with early and persistent pulmonary dysfunction (EPPD group: FiO₂ consistently ≥ 0.23 on all days between 3 and 7 postnatal days and receiving FiO₂ > 0.25 on Day 14).¹ There were no patients with an FiO₂ > 0.23 on any day between 3 and 7 postnatal days and receiving < 0.25 on Day 14, so this group was not included. The diagnosis of CLD was based on whether or not the child was receiving supplemental oxygenation at 36 weeks PMA.

Demographic, Pregnancy and Neonatal Variables

Pregnancy characteristics and data describing newborns at the time of delivery included maternal race, receipt of antenatal steroids, chorioamnionitis, pregnancy complications, multi-fetal pregnancy, gender, gestational age, and birth weight. The birth weight Z-score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in a standard data set.³

The SNAP-IITM (Score for Neonatal Acute Physiology-II)⁴ was calculated from measures taken during the first 12 hours of life. Mode of ventilation was defined as the highest level of support on each day and ranged from no support, supplemental oxygen by hood or nasal cannula, nasal continuous positive airway pressure, and conventional mechanical ventilation to high frequency ventilation and was recorded on days 0–7, 14, 21, and 28, and at 36 weeks PMA. We also recorded the number of days each infant received supplemental oxygen, CPAP, and conventional mechanical ventilation (including high frequency ventilation). Diagnoses of pneumothorax, pulmonary interstitial emphysema, and pulmonary hemorrhage were those made by the clinicians caring for the infant.

Confirmed early bacteremia was defined as recovery of an organism from blood drawn during the first postnatal week, and confirmed late bacteremia as recovery of an organism

from blood drawn during the second, third or fourth week. Confirmed tracheal colonization required the recovery of a pathogen from tracheal aspirate.

The diagnosis of PDA was made by clinicians using their own operational definitions, which might or might not have included echocardiographic findings. We did not record the day of diagnosis. We recorded whether the PDA was ligated and whether indomethacin was offered as medical therapy. If a child had surgical ligation of the PDA, the infant was assigned to the surgical therapy group only, even if the infant first received medical therapy. Infants classified as having received medical therapy received indomethacin and did not have the PDA ligated.

The presence of chorioamnionitis and funisitis was determined by an ELGAN study pathologist at each institution who first engaged in training procedures to minimize inter-observer variability, was masked to maternal history, and used pre-defined operational definitions; 1126 placentas were examined.⁵⁶

Medications were recorded if given on any day during the first week through fourth weeks, and included surfactant, analgesics (i.e., morphine, fentanyl, or methadone), sedatives (i.e., lorazepam, midazolam, or chloral hydrate), vitamin A, and steroids (i.e., hydrocortisone and dexamethasone). Indications were not recorded.

Data Analysis

We evaluated whether groups of antecedents of CLD differed among the three early respiratory pattern groups. First we calculated risks of CLD among infants classified by their early respiratory pattern and the presence or absence of other characteristics and exposures. The characteristics that most clearly distinguished infants at highest risk of CLD from their peers were then included in logistic regression models to assess the strength of association of each characteristic/exposure to the risk of CLD within each early respiratory pattern group, while adjusting for other factors included in the regression. Gestational age categories (23–24, 25–26, 27 weeks) and birth weight Z-score groups (<-2, -2 but <-1, -1)⁷⁸ were included in every multivariable model.

Because postnatal phenomena, such as the need for ventilatory assistance, can be influenced by antepartum phenomena, we created logistic regression models in which risk factors are ordered in a temporal pattern, so that the earliest occurring predictors/covariates of an outcome (e.g., CLD) are entered first and are not displaced by later occurring covariates work.^{9–14} For these time-oriented risk models (TORMs), we categorize sets of antecedents/covariates by the time they occur or are identified. We grouped prenatal and birth characteristics and exposures into the antenatal epoch, all exposures and characteristics during the first week into the early neonatal epoch, and exposures and characteristics occurring or reported between weeks 2–4 into the late neonatal epoch. We included in the antenatal epoch a hospital stratum (group) term to account for the possibility that infants born at a particular hospital are more like each other than like infants born at other hospitals.¹⁵ Because the risk of CLD among infants born with a sibling did not differ from that of singletons, we did not adjust for number of fetuses.

We used a step down procedure within each epoch, seeking a parsimonious solution without interaction terms. After the antenatal epoch variables were identified, the early neonatal variables were added. We then dropped non-significant neonatal variables but did not permit displacement of antenatal variables. Finally, the late neonatal epoch variables were added to the reduced antenatal/early neonatal set and non-significant late neonatal variables dropped. The contributions of relevant variables in the final model are presented as odds ratios with 95% confidence intervals. We created three TORMs of CLD, one for each pattern of early respiratory function.

RESULTS

Among 1506 infants enrolled in the ELGAN Study, 1204 survived to 36 weeks PMA and constitute the cohort for this study (Figure). The early respiratory function was categorized as EPPD in 42% (n=508) of the infants, as PD in 38% (n=456), and as Low FiO₂ in 20% (n=240). The incidence of CLD varied among groups defined by these respiratory patterns during the first two postnatal weeks. CLD was diagnosed in 69% of infants in the EPPD group, 52% in the PD group, and 17% in the Low FiO₂ group.

Univariate Analyses

Antenatal factors [Table 1]—Lower gestational age and lower birth weight were associated with an increased risk of CLD in all respiratory-pattern groups. Lower birth weight z-scores were associated with an increased risk of CLD in all groups, particularly in the Low FiO₂ group. In this group, 38% of infants with a birth weight Z-score between -2 and -1 and 70% of infants with a birth weight Z-score of < -2 developed CLD, compared to 13% among appropriate for gestational age birth weight infants. Among infants in the Low FiO₂ group, those delivered for maternal indications (preeclampsia) were at an increased risk of CLD (40%, compared to 10–19% among other indications for delivery). In the PD group, male infants were more likely to develop CLD (56% vs. 47% among female infants). Aside from gestational age, birth weight and birth weight z-score, no antenatal characteristic or exposure among infants in the EPPD group conveyed information about the risk of CLD.

Early neonatal factors [Table 2]—A SNAP-II™ greater than 30 and receipt of mechanical ventilation on postnatal day 7 were associated with an increased risk of CLD in all groups. In the Low FiO₂ group, receipt of dexamethasone, vitamin A, analgesics, and sedation were associated with an increased risk of CLD. In the PD group, receipt of surfactant, hydrocortisone, dexamethasone, and analgesics, as well as confirmed bacteremia and tracheal infection, were associated with an increased risk of CLD. In the EPPD group, receipt of surfactant was associated with an increased risk of CLD and receipt of dexamethasone, sedation, and vitamin A were associated with a decreased risk of CLD.

Late neonatal factors [Table 3]—In all groups, infants who received dexamethasone, analgesics, or sedation, as well as those who were ventilated on day 14 or 21, had confirmed tracheal infection, developed pneumothorax or isolated intestinal perforation, were at increased risk of CLD. In the Low FiO₂ group, receipt of hydrocortisone and vitamin A, or required surgery for necrotizing enterocolitis were associated with an increased risk of CLD.

Infants in the PD group were at increased risk of CLD if they received hydrocortisone, had confirmed bacteremia, or required surgery for necrotizing enterocolitis. In the EPPD group, confirmed bacteremia and PDA were associated with an increased risk, and receipt of vitamin A was associated with a decreased risk of CLD.

Placenta histology and microbiology [Table 4]—Thrombosis of fetal stem vessels, infarcts, and increased syncytial knots were associated with an increased risk of CLD, and this was most pronounced in the Low FiO₂ group. In all groups, no organism or group of organisms recovered from the placenta conveyed information about CLD risk (data not shown).

Time Oriented Risk Models [Table 5]

Low FiO₂ group—In the Low FiO₂ group, birth weight z-score < -1 was associated with an increased risk of CLD. In the early neonatal epoch, only SNAP-IITM >30 was associated with an increased risk of CLD, while receipt of surfactant was associated with a reduced risk. In the late neonatal epoch, receipt of analgesics was associated with an increased risk of CLD. The presence of pulmonary interstitial emphysema was also associated with increased risk; however, this diagnosis was assigned to only six infants.

PD group—Infants in the PD group were at increased risk of CLD if their gestational age was < 27 weeks, their birth weight Z-score was < -1, and they were male. In the early neonatal epoch, SNAP-IITM >30, definite bacteremia, and mechanical ventilation on day 7 were associated with an increased risk of CLD, while a diagnosis of pneumothorax in the late neonatal epoch was associated with an increased risk of CLD.

EPPD group—Among infants in the EPPD group, those whose gestational age was 23–24 weeks, had a birth weight Z-score of < -1 were at increased risk of CLD. Delivery for preeclampsia or a fetal indication approached nominal statistical significance. Only mechanical ventilation on day 7 entered in the early neonatal epoch, while two late neonatal variables, pulmonary interstitial emphysema and receipt of hydrocortisone, provided additional information about an increased risk of CLD.

DISCUSSION

In this study, we evaluated CLD risk factors in three groups of infants characterized by their pulmonary function during the first two weeks after birth. These groups differed in their likelihood of developing CLD. Differences in early exposure to oxygen might not only have defined these three groups, but also influenced CLD risk. However, we hypothesized that each group had its own risk profile for CLD that included factors not directly related to pulmonary function or therapies. We were particularly interested in antecedents of CLD among infants with little exposure to increased concentrations of oxygen during early life (the Low FiO₂ group). Although multiple factors were significant in univariate analysis (e.g., vitamin A), once adjustments were made in multivariate analysis, many of these were no longer significant.

In a previous report, we demonstrated that fetal growth restriction was the antenatal factor that best predicted CLD.¹⁶ In the current study, fetal growth restriction was associated with increased CLD risk in all groups defined by early pulmonary function, even after adjustment for early and late postnatal neonatal exposures and other morbidities. The observation that this effect was most pronounced in the Low FiO₂ group suggests that processes that limit fetal growth might predispose to abnormal lung growth before and after birth, ultimately resulting in pulmonary dysfunction. This cascade of events appears to occur even in the absence of exposures likely to result in lung injury.

Severe growth restriction might contribute to CLD risk in several ways. First, factors that impair fetal somatic growth might also impair lung development, resulting in abnormal development of terminal air sacs and alveoli, or abnormal pulmonary angiogenesis.¹⁷ This might be similar to the changes characteristic of the "new BPD".^{18,19}

Second, an imbalance between angiogenic and anti-angiogenic factors might disrupt normal placental angiogenesis and abnormal fetal angiogenesis, including the vasculature of the fetal lung. Preeclampsia is the disorder most closely associated with fetal growth restriction and is also associated with disturbed angiogenesis.²⁰ Our observation of an increased risk of CLD among those whose placenta had increased syncytial knots, a histologic abnormality characteristic of preeclampsia, supports this possibility.

Third, chronic fetal hypoxia, sometimes identified as a factor that impairs growth²¹, might be accompanied by impaired lung development. This possibility is supported by observations from animal studies. Impaired alveolar and pulmonary artery development occurs in neonatal mice exposed to chronic hypoxia during the first two weeks of life, a period of lung development that corresponds to human fetal lung development during the third trimester.²² Regardless of the mechanism, the interaction between factors that control fetal somatic growth and lung maturation is complicated.

Fetal growth restriction also was associated with CLD in the PD group and to a lesser extent in the EPPD group. In the PD group, characteristics associated with gestational age and male gender appear to have influenced CLD risk. In addition, among neonatal exposures, mechanical ventilation was most influential. Although gestational age and FGR were important in the EPPD group, mechanical ventilation at 7 days and dexamethasone treatment in the late neonatal period were the factors most strongly associated with CLD. The latter association probably reflects selective use of this therapy in infants likely to develop CLD. PIE was also associated with increased risk. These observations suggest that even in the absence of vulnerability imparted by growth restriction, infants with PD are particularly vulnerable to CLD due to extreme immaturity or exposures that injure the lung (e.g. high oxygen concentrations and mechanical ventilation).

In the Low FiO₂ group and EPPD group, exposure to analgesics and dexamethasone, respectively, during the late neonatal period was associated with an increased risk of CLD. For the Low FiO₂ group, one possibility is that analgesic use itself renders an infant more likely to develop CLD, directly or through secondary effects. Narcotics, such as morphine, depress the respiratory drive and might therefore prolong the need for mechanical

ventilation and, thus, increase the risk of ventilator-induced lung injury. In a randomized controlled trial²³, infants treated with mechanical ventilation who were allocated to receive continuous morphine infusions were ventilated for one week longer than infants allocated to placebo.²⁴ Another explanation for this observation is that exposure to analgesics or dexamethasone is indicative of greater illness severity or longer duration of mechanical ventilation. A more valid conclusion about dexamethasone is available from meta-analyses of randomized, placebo controlled trials,²⁵²⁶ which indicate that this treatment reduces the risk of CLD. The decision to treat an infant with an analgesic or to ventilate an infant might reflect the physician's perception that the infant is sufficiently ill to require these therapies, rather than analgesics or ventilation contributing to CLD risk. Alternatively, many infants treated with mechanical ventilation receive analgesics, for sedation. This is an example of confounding by indication, a problem common to many epidemiologic studies incorporating clinical decisions as variables, outcomes or exposures.²⁷²⁸ For example, later-occurring conditions or events, such as necrotizing enterocolitis or PDA ligation, might both require treatment with narcotic analgesics and increase the risk of CLD through pathogenic mechanisms not involving the medication.

Intra-amniotic inflammation has been implicated in the development of so-called atypical CLD (i.e. CLD not preceded by respiratory distress syndrome).²⁹ All infants in our Low FiO₂ group and many infants in our PD group would have been classified as having atypical CLD using this definition. We found no association between CLD and either histologic markers of placental inflammation or microbiologic evidence of placental infection and CLD in groups defined by their early lung function. Our data suggest that intrauterine infection is unlikely to be a risk factor for CLD, regardless of the presence or absence of early respiratory disease. Chorioamnionitis has been inconsistently reported as affecting respiratory outcomes (respiratory distress syndrome and CLD)³⁰³¹, most likely because the diagnosis of chorioamnionitis is challenging and does not provide information about the organism, duration, or extent of fetal involvement. One possibility that we did not find an association is that respiratory care practices in ELGAN centers might have attenuated the putative pathway to CLD that involves intrauterine inflammation followed by postnatal ventilator-induced lung injury.³¹

We did not observe a relationship between severe NEC and CLD risk, as has been reported previously.³²³³ One explanation for the difference in these findings is that our sample size permitted adjustment for a large number of confounders and antecedents. Another is that antenatal phenomena contributed to both CLD and NEC, but by our use of time oriented regression modeling we reduced the probability of perceiving an epiphenomenon (such as NEC) as a risk factor.

Conclusion

The risk of CLD varies among infant groups defined by their pulmonary function during the first two postnatal weeks. Among infants with little exposure to oxygen during this period, FGR is the factor most strongly associated with CLD. Among infants with PD or EPPD, other factors, such as gestational age, male gender, and mechanical ventilation also convey nearly as much or more information about CLD risk. Therefore, CLD among infants with

little exposure to oxygen early in life might result almost exclusively from fetal phenomena related to lung growth. These observations have the potential to inform future investigations of the biological mechanisms underlying the association between patterns of early pulmonary function and the development of CLD.

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Abbreviations

PD	pulmonary deterioration
ELGAN	extremely low gestational age newborn
CLD	chronic lung disease
PDA	patent ductus arteriosus
EPPD	early and persistent pulmonary dysfunction
SNAP	score for Neonatal Acute Physiology
FGR	fetal growth restriction
PTX	pneumothorax
PMA	post-menstrual age
PE	preeclampsia
pPROM	prolonged, premature rupture of membranes
FI	fetal indication
PTL	preterm labor
BW	birth weight

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"What is already known on this topic" –Pulmonary dysfunction in the first two postnatal weeks in preterm infants can be characterized into three groups by the fraction of inspired oxygen they require. The risk of chronic lung disease varies among infant groups defined by their pulmonary function during the first two postnatal weeks.

"What this study adds" –Among infants with little exposure to oxygen during this period, fetal growth restriction is the factor most strongly associated with chronic lung disease. Among infants with pulmonary deterioration or early and persistent pulmonary dysfunction, other factors, such as gestational age, male gender, and mechanical ventilation convey nearly as much or more information about chronic lung disease risk as fetal growth restriction.

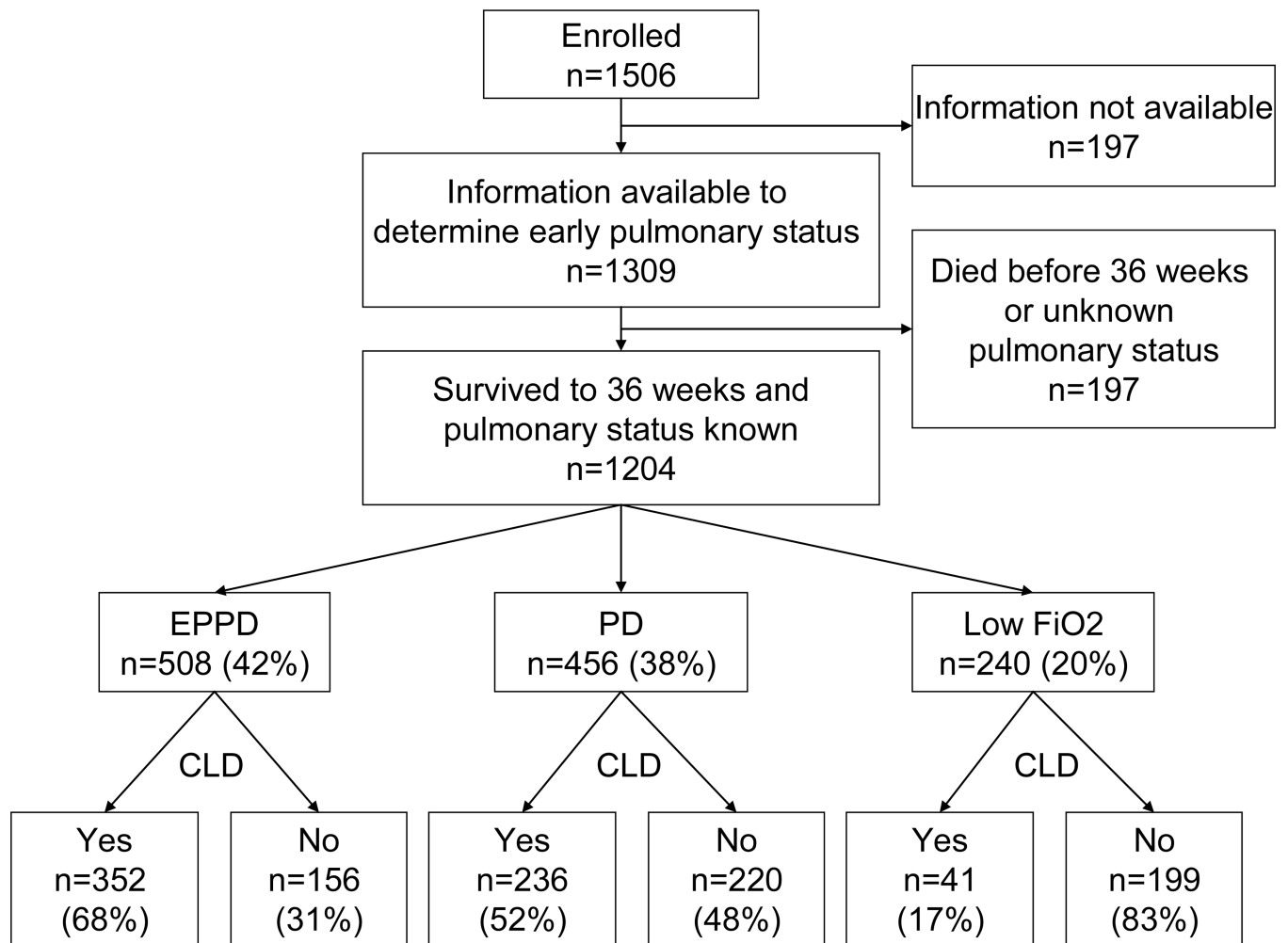


Figure 1.

Derivation of cohort. EPPD=early and persistent pulmonary dysfunction (an FiO_2 consistently ≥ 0.23 on all days between 3 and 7 postnatal days and receiving $\text{FiO}_2 > 0.25$ on Day 14); PD=Pulmonary Deterioration (an $\text{FiO}_2 < 0.23$ on any days between 3 and 7 days and receiving $\text{FiO}_2 > 0.25$ on day 14); Low FiO_2 =consistently low FiO_2 (an FiO_2 consistently < 0.23 on all days between 3 and 7 postnatal days and receiving $\text{FiO}_2 \geq 0.25$ on Day 14). CLD=chronic lung disease among survivors.

Table 1

Univariate associations between antenatal factors and the risk of chronic lung disease (CLD). The right-most column provides the maximum number of infants with the attribute listed in each row; any differences are due to missing data. All other data are the percentage of infants with CLD among those infants with the attribute listed on the two left columns and the respiratory patterns listed as column headings. For example, among infants with a gestational age of 23–24 weeks who had the Low FiO₂ respiratory pattern, the prevalence of CLD was 30%.

Antenatal factors	Respiratory Pattern			Row N	
	Low FiO ₂	PD*	EPPD*		
Gestational age (weeks)	23–24	30	76	85	250
	25–26	19	57	64	560
	27	15	33	62	394
Birth weight (g)	750	41	74	81	461
	751–1000	14	43	58	512
	> 1000	11	29	51	231
Birth weight Z-score	< -2	70	68	86	75
	-2 to -1	38	70	80	163
	-1	13	47	65	966
Sex	Male	18	56	69	638
	Female	16	47	69	566
Antenatal steroid	Complete	17	50	71	767
	Partial	16	56	67	316
	None	21	53	64	117
Number of fetuses	Single	18	53	69	819
	Multiple	16	50	69	385
Cesarean delivery	Yes	16	54	70	804
	No	24	48	68	400
Delivery indication	PTL	15	49	67	526
	pPROM*	12	52	67	265
	Preeclampsia	40	64	74	163
	Abruption	19	48	73	126

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Antenatal factors	Respiratory Pattern			Row N
	Low FIO ₂	PD*	EPPD*	
Cervical Insufficiency	13	45	57	72
Fetal indication	10	67	85	52
Percent CLD	17	52	69	52
Maximum Column N	240	456	508	1204

* PD=pulmonary deterioration, EPPD=early and persistent lung dysfunction, pPROM=prolonged, premature rupture of membranes

Table 2

Univariate associations between early neonatal factors and the risk of chronic lung disease (CLD). The right-most column provides the maximum number of infants with the attribute listed in each row; any differences are due to missing data. All other data are the percentage of infants with CLD among those infants with the attribute listed on the two left columns and the respiratory patterns listed as column headings. For example, among infants with a SNAP-II score 19 who had the Low FiO₂ respiratory pattern, the prevalence of CLD was 16%.

Early neonatal factors	Respiratory Pattern			Row N	
	Low FiO ₂	PD	EPPD		
SNAP-II™*	19	16	42	61	622
	20-29	17	57	72	303
	30	31	74	76	260
Surfactant	Yes	17	55	70	1083
	No	18	28	63	121
Hydrocortisone	Yes	20	70	69	89
	No	17	50	69	1115
Dexamethasone	Yes	33	75	61	12
	No	17	52	70	1192
Analgesic	Yes	23	61	69	664
	No	13	43	69	540
Sedation	Yes	26	54	59	174
	No	16	51	72	1030
Vitamin A	Yes	26	48	66	342
	No	15	53	71	862
Confirmed bacteremia	Yes	20	66	65	73
	No	17	51	70	1130
Confirmed tracheal infection	Yes	0	62	68	48
	No	18	52	70	1147
Mechanical ventilation** (day 7)	Yes	29	68	75	726
	No	14	30	42	477
Percent CLD*		17	52	69	52
Maximum Column N		240	456	508	1204

SNAP-IITM=Score for Neonatal Acute Physiology, PD=pulmonary deterioration, EPPD=early and persistent pulmonary dysfunction, CLD=chronic lung disease

** Mechanical ventilation includes conventional mechanical ventilation and high frequency ventilation

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Univariate associations between late neonatal factors and the risk of chronic lung disease (CLD). The right-most column provides the maximum number of infants with the attribute listed in each row; any differences are due to missing data. All other data are the percentage of infants with CLD among those infants with the attribute listed on the two left columns and the respiratory patterns listed as column headings. For example, among infants who received hydrocortisone that had the Low FiO₂ respiratory pattern, the prevalence of CLD was 40%.

Table 3

Late neonatal factors		Respiratory Pattern			Row N
		Low FiO ₂	PD*	EPPD*	
Hydrocortisone	Yes	40	76	69	142
	No	17	40	69	1062
Dexamethasone	Yes	50	74	86	78
	No	17	51	67	1126
Analgesic	Yes	27	66	75	578
	No	14	39	60	626
Sedation	Yes	32	63	74	264
	No	16	49	67	940
Vitamin A	Yes	21	50	65	354
	No	16	52	72	850
Confirmed bacteremia	Yes	16	63	73	298
	No	17	48	68	905
Confirmed tracheal infection	Yes	28	63	74	230
	No	17	49	68	964
Mechanical ventilation(day 14)**	Yes	31	72	77	717
	No	14	26	36	486
Mechanical ventilation(day 21)**	Yes	43	72	77	696
	No	12	27	39	504
Patent ductus arteriosus (PDA)	Yes	20	58	71	798
	No	14	40	64	406
Pneumothorax (PTX)	Yes	25	73	81	91
	No	17	50	68	1113

Late neonatal factors	Respiratory Pattern			Row N
	Low FIO ₂	PD*	EPPD*	
Pulmonary interstitial emphysema (PIE)	Yes	79	85	189
	No	49	63	1015
Necrotizing Enterocolitis ^{***}	No/Stage I, II	50	69	1009
	Stage IIIa	67	50	13
	Stage IIIb	92	68	48
	Isolated perf	71	88	34
Percent CLD	17	52	69	52
Maximum Column N	240	456	508	1204

* PD=pulmonary deterioration, EPPD=early and persistent pulmonary dysfunction

** Includes conventional mechanical ventilation and high frequency ventilation

*** Bell's staging

Table 4

Univariate associations between placenta histologic characteristics and the risk of chronic lung disease (CLD). The right-most column provides the maximum number of infants with the attribute listed in each row; any differences are due to missing data. All other data are the percentage of infants with CLD among those infants with the attribute listed on the two left columns and the respiratory patterns listed as column headings. For example, among infants who had inflammation of the chorionic plate that had the Low FIO₂ respiratory pattern, the prevalence of CLD was 12%.

Placenta histology	Respiratory pattern			Row N
	Low FIO ₂	PD*	EPPD*	
Inflammation chorionic plate**	Yes	48	75	212
	No	19	69	895
Inflammation chorion/deciduas***	Yes	8	75	411
	No	25	67	696
Neutrophilic infiltration fetal stem vessels	Yes	15	81	274
	No	19	67	814
Umbilical cord vasculitis****	Yes	11	73	181
	No	20	70	901
Thrombosis of fetal stem vessels	Yes	40	77	58
	No	17	70	1039
Infarct	Yes	32	75	190
	No	15	69	927
Increased syncytial knots	Yes	40	76	223
	No	13	69	898
Decidual hemorrhage/fibrin deposition	Yes	25	72	182
	No	17	70	923
Percent CLD*	18	52	70	52
Maximum Column N	227	429	470	1026

* PD=pulmonary deterioration, EPPD=early and persistent pulmonary dysfunction, CLD=chronic lung disease

** stage 3 and severity 3

*** grades 3 and 4

**** grades 3, 4 and 5

Table 5

Odds ratios and 95% confidence intervals obtained with time-oriented risk models of chronic lung disease for three patterns of respiratory disease (Low FiO₂, Pulmonary Deterioration [PD], or Early and Persistent Pulmonary Dysfunction [EPPD]) during the first four postnatal weeks.

1. Antenatal	Low FiO₂	PD	EPPD
GA 23–24 wks		3.2 (2.0, 8.8)	2.5 (1.5, 4.3)
GA 25–26 wks		1.9 (1.1, 3.1)	
BW Z-score < -1	26 (7.0, 95)	4.4 (2.3, 8.2)	2.0 (1.1, 3.9)
Male		1.9 (1.2, 3.1)	
Cesarean delivery	0.5 (0.2, 1.2)		
Indication is PE or FI			1.9 (0.98, 3.8)
2. Early neonatal (week 1)			
SNAP-II™ 30+	3.3 (1.02, 11)	2.0 (1.1, 3.9)	
Definite bacteremia		2.6 (1.01, 6.9)	
Surfactant	0.2 (0.1, 0.7)		
Mechanical ventilation on day 7	1.5 (0.5, 3.9)	4.2 (2.5, 6.9)	2.7 (1.5, 4.7)
3. Late neonatal (weeks 2–4)			
Dexamethasone			3.0 (1.2, 7.2)
Analgesic	3.4 (1.2, 9.5)		
PTX		1.9 (1.1, 3.2)	
PIE	17 (2.1, 140)		2.6 (1.5, 4.6)

Variables offered:

Antenatal epoch: gestational age 23–24 weeks, gestational age 25–26 weeks, birth weight Z-score, sex, complete course of antenatal steroids, multiple birth, cesarean delivery, delivery for preeclampsia or fetal indication, thrombosis of the fetal stem vessels in the placenta

Early neonatal epoch (week 1): SNAP-IITM 30, confirmed early bacteremia, confirmed tracheal infection, receipt of surfactant, hydrocortisone, dexamethasone, analgesic, sedation, or vitamin A, mechanical ventilation

Late neonatal epoch (weeks 2–4): confirmed bacteremia, confirmed tracheal infection, receipt of hydrocortisone, dexamethasone, analgesics, sedation, or vitamin A, patent ductus arteriosus, pneumothorax, pulmonary interstitial emphysema