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Chronic lung disease in Saudi preterm infants

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Abstract
Background: Despite advances in neonatal medicine, chronic lung disease (CLD) remains a major cause of pulmonary morbidity in preterm infants.
Objective: To determine the prevalence of CLD and to identify the possible risk factors that may predict the development of CLD.
Patients and Methods: A retrospective study of preterm infants admitted to the NICU between July 2011 and June 2022 with gestational age (GA) < 32 weeks and birth weight (BW) < 1500 g was performed.
Results: A total of 706 preterm infants were included in the study, of whom 202 (28.6%) infants developed CLD. Of the 202 preterm infants who developed CLD, 194 survivors; 93 (47.9%) had mild, 58 (29.9%) had moderate and 43 (22.2%) had severe CLD. Multivariate analysis showed that low GA (odds ratio [OR]: 0.62; 95% confidence interval [CI]: 0.43-0.98), low BW (OR: 20.6; 95% CI: 17.1-29.3), use of mechanical ventilation (OR: 1.07; 95% CI: 0.87-1.54), higher peak inspiratory pressure (PIP) (OR: 1.48; 95% CI: 1.44-1.91), higher fraction of inspired oxygen (FiO_2) use (OR: 0.11; 95% CI: 0.05-0.19), duration of mechanical ventilation (OR: 3.56; 95% CI: 4.28-3.75) and frequent blood transfusion (OR: 0.65; 95% CI: 0.53-0.87) were identified as the main risk factors for the development of CLD.
Conclusions: The prevalence of CLD among preterm infants was 28.6%. The most relevant predictors of CLD were GA, BW, mechanical ventilation, higher PIP, higher FiO_2 use, duration of mechanical ventilation and frequent blood transfusion.

Keywords: Preterm infants, chronic lung disease, predict

Introduction
Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) is an important cause of respiratory illness in preterm infants that results in high morbidity and mortality [1]. Advances in neonatal care results in increased survival rate of preterm newborn infants however, the incidence of CLD remains high [2, 3]. CLD results from complications related to the lung injury during the aggressive mechanical ventilation during the treatment of respiratory failure in extreme preterm infants [4, 5].
The Pathogenesis of CLD is multifactorial including genetic predispositions in combination with environmental factors [6]. The risk factors for CLD include birth weight (BW), gestational age (GA), male sex, and invasive mechanical ventilation [7].
Because survivors with CLD have significant pulmonary and extrapulmonary morbidities, including cerebral palsy, and growth, developmental, and academic difficulties, it is imperative to optimize health care delivery systems. Identification of risk factors would possibly allow for better practices targeting the reduction of the severity of CLD and favorable outcomes [8-11].
There is little data about the epidemiology and pathogenesis of CLD in developing countries [12]. This study was conducted to determine CLD incidence and to identify factors that may predict the development of CLD in Saudi preterm infants.

Patients and Methods
This study was conducted at the neonatal intensive care unit (NICU) of Abha Private Hospital, Abha, Saudi Arabia during an 11-year period between July 2011 and June 2022. The inclusion criteria include preterm (< 32 weeks) and very low birth weight (VLBW, <

1500 g) preterm infants. The exclusion criteria were congenital diaphragmatic hernia, congenital infections, chromosomal abnormalities, or other congenital malformation.

Data collection

In the current retrospective study, reviewing data collected through medical records of premature infants was performed. The collected neonatal data included gestational age (GA), birth weight (BW) gender, Apgar score at 1 and 5 minutes, pre and postnatal steroids administration, invasive and non-invasive mechanical ventilation, nasal continuous positive airway pressure (CPAP), oxygen (O_2) supply, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), pulmonary hypertension (PHN), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), frequent blood transfusion ($\geq$ 3 times).

Definition of BPD (CLD)

The definition of BPD (CLD) was as follow: no BPD if the patient did not getting O_2 for 28 days or at 36 weeks postconceptional age (PCA); mild BPD if received O_2 for $\geq$ 28 days but not at 36 weeks PCA; moderate BPD if received O_2 for $\geq$ 28 days in addition to treatment with < 30% O_2 at 36 weeks PCA; and severe BPD if received O_2 for $\geq$ 28 days in addition to treatment with $\geq$ 30% O_2 or positive pressure at 36 weeks PCA [13].

Clinical practice

In the last decade, we changed our practice from invasive to non-invasive ventilation including the use of nasal CPAP, lung protective ventilation targeting O_2 saturation from 88-92%. A selective intubation policy in the delivery room for infants at $\leq$ 28 weeks of gestation was added to our guidelines.

Statistical analysis

Statistical analysis was performed using the Statistical Software Package SPSS 20 (SPSS, Inc., Chicago, IL). Qualitative data were demonstrated as frequency and percent (%) while Quantitative data were presented as mean $\pm$ standard deviation (SD). Non-parametric data were assessed by chi-square test. The significance of comparison between mean values of two groups was tested by Student's *t*-test. The significance of comparison between more than two groups was performed by analysis of variance for parametric continuous variables. Crude and adjusted odds ratio (OR) with 95% confidence intervals (95% CIs) were estimated in bivariate analysis, followed by multivariate regression analysis to explore associations between the risk factors and CLD. Significant differences were detected by $p < 0.05$.

Results

This study included 795 preterm infants (< 32 weeks) and BW of (<1500 g) who were admitted to the NICU. Eighty-nine infants were excluded from the analysis (48 had congenital malformations, 28 died before 36 weeks PMA and 13 missing data). Seven hundred and six premature infants fulfilled the criteria for inclusion in the study, of whom 202 (28.6%) infants developed CLD (Figure 1).

The perinatal, neonatal demographic, clinical characteristics and respiratory management are shown in tables 1,2 and 3. Birth weight, gestational age, and Apgar score at 1 minute were significantly lower in patients who developed CLD than in those without CLD. In term of maternal risk factors, the prevalence of chorioamnionitis was significantly higher in infants who had developed CLD (p = 0.03). In infants who developed CLD, 86.6% had RDS, 76.2% were on invasive type of mechanical ventilation and 42.1% were on noninvasive ventilation (Nasal CPAP). In preterm infants who developed CLD, the duration of mechanical ventilation and O_2 supply were 19.3 and 45.6 days, respectively, which were significantly longer than those in the same supportive measures for preterms who had not developed CLD. The common complications of prematurity were more frequent in the CLD group, who were also younger gestational age and lower birth weight. In terms of co-morbidities, we looked for [sepsis, patent PDA, PHN, IVH, ROP and NEC, only IVH and frequent blood transfusion were significantly associated with CLD [p=0.03, OR = 2.1, CI = 1.06-3.95; p <0.001, OR= 0.44, CI =0.40-0.57, respectively].

Two-hundred and two preterm neonates developed CLD. Of whom, 194 survivors; 93 (47.9%) had mild, 58 (29.9%) had moderate and 43 (22.2%) had severe CLD. As the gestational age and birth weight were lower, the duration of mechanical ventilation, oxygen therapy was longer and maximum peak inspiratory pressure (PIP) was higher as the CLD severity increased (table 4).

The Univariate analysis indicated that low gestational age, low birth weight, presence of chorioamnionitis, low Apgar score at 1 minute, presence of pneumothorax, IVH, the use of mechanical ventilation with high level of PIP, longer period of invasive mechanical ventilation, period of oxygen therapy and blood transfusion were significantly associated with increased risk of CLD (table 5). Multivariate logistic regression analysis demonstrates that gestational age, birth weight, mechanical ventilation, higher PIP, higher fraction of inspired oxygen (FiO_2) use, duration of mechanical ventilation and frequent blood transfusion were identified as the main risk factors for CLD (Table 6).

Discussion

Chronic lung disease is one of the most common complications of prematurity despite advances in neonatal care [5]. The CLD incidence observed in our study was 28.6% which is in agreed with that concluded by Alshehri [12] and Mohamed *et al.* [14] in the same region. In comparison with our results, the incidence of CLD in preterm infants admitted to NICU at lower altitude (Riyadh city, Saudi Arabia) was lower (17.7%). These results suggest that high altitude may be associated with the increased risk of development of CLD preterm neonates [12].

Our data demonstrated that lower GA, lower BW and lower one-minute Apgar score were risk factors related to the development of CLD. These findings are in accordance with that reported by previous studies [15-17]. The prevalence of CLD in preterm neonates is inversely related to the gestational age and birth weight. The development of the lung is completed after birth, preterm delivery makes the lung more susceptible to environmental factors that disrupt this development resulting in CLD [18-20].

Stevenson and his co-authors reported that male gender, prolonged rupture of membranes and antenatal corticosteroids use are risk factors for CLD, these findings are in contrast with ours that did not detect any significant differences [21]. Our data demonstrated that chorioamnionitis was significantly associated with increased risk of CLD

development which might be attributed to inflammatory processes and disturbance of lung development [22].

Our results did not find a relationship between co-morbidities as neonatal sepsis, PDA, PHN, ROP NEC, BPD and CLD which is in contrast with other reports [23-25]. However, IVH and frequent blood transfusion were significantly associated with CLD in the present study. Frequent blood transfusion may increase free iron that can give rise to formation of oxygen derived- free radical and oxidative injury to the lung resulting in CLD [26].

In term of respiratory management of preterm infants, the present study demonstrated that the use of mechanical ventilation, higher PIP, longer duration of assisted ventilation, use of higher FiO_2, longer duration of oxygen therapy, less use of nasal CPAP and the less administration of caffeine were significantly associated with the development and severity of CLD. This agrees with previous publications [23-25]. Our data support the hypothesis that the use of high PIP in invasive mechanical ventilation may result in pneumothorax and increased production of pro-inflammatory cytokines causing pulmonary injury that led to the development of CLD [27, 28].

Non-invasive ventilator support such as nasal CPAP provides stability of airways and decreasing work of breathing thus reduces the need for invasive mechanical ventilation which is a major risk factor for CLD therefore, early use of nasal CPAP may reduce the incidence of CLD [29]. Caffeine is an effective treatment of apnea of prematurity and decreases the use of mechanical ventilation, therefore, reduces the rate of CLD in preterm neonates [30].

In the present study, multivariate logistic regression analysis demonstrated that GA, BW, mechanical ventilation, higher PIP, higher FiO_2 use, duration of mechanical ventilation and frequent blood transfusion were linked to increased risk of CLD. A retrospective study is a limitation of the study so prospective trials should be considered.

Table 1: Clinical and demographic characteristics of preterm infants with or without chronic lung disease of prematurity (CLD)

Variables	CLD (n=202)	No CLD (n=504)	*P* value
BW (g)[a]	1022±91	1057±109	<0.001
GA (Wk)[a]	28.1±0.7	29.2±1.8	< 0.001
Male gender [b]	106 (52.5)	259 (51.4)	0.79
Maternal age (y)[a]	26.3±2.4	26.1±3.6	0.47
Twin or multiple births [b]	9 (4.5)	23 (4.6)	0.16
Antenatal steroids [b]	160 (79.2)	416 (82.5)	0.31
PROM [b]	31 (15.3)	84 (16.7)	0.67
Chorioamnionitis [b]	40 (19.8)	27 (5.4)	0.03
Caesarian section [b]	54 (26.7)	128 (25.4)	0.71
Apgar score at 1 min[a]	4.7±0.5	4.9±0.7	0.001
Apgar score at 5 min[a]	6.4±0.7	6.5±0.9	0.06

[a] Values are mean ± SD

[b] Number (percent)

GA; gestational age, BW; birth weight, PROM; prolonged rupture of membranes >18 hr

$p<0.05$; significant

Table 2: Neonatal diseases and co-morbidities with the presence of CLD

Variables	CLD (N=202)	No CLD (N=504)	*P* value
RDS [a]	175 (86.6)	440 (87.3)	0.81
Pneumothorax [a]	21 (10.4)	27 (5.4)	0.02
Pneumonia [a]	32 (15.8)	83 (16.5)	0.83
Sepsis [a]	60 (29.7)	157 (31.2)	0.71
PDA [a]	18 (8.9)	44 (8.7)	0.93
PHN [a]	17 (8.4)	42 (8.3)	0.97
IVH [a]	19 (9.4)	24 (4.8)	0.02
ROP [a]	9 (4.5)	16 (3.2)	0.40
NEC [a]	25 (12.4)	44 (8.8)	0.14
Frequent blood transfusion [b]	3.3 ± 1.2	2.9 ± 0.9	0.000
Duration of hospitalization [b]	64.5 ± 3.1	46.5 ± 3.8	<0.001
Mortality [a]	7 (3.5)	12 (2.4)	0.42

[a] Number (percent)

[b] Values are mean ±SD

Respiratory distress syndrome; RDS, PDA; patent ductus areriosus, PHN; pulmonary hypertension, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity, NEC; necrotizing enterocolitis

$p<0.05$; significant

Table 3: Respiratory management for the studied groups

Variables	CLD (n=202)	No CLD (n=504)	*P* value
Surfactant therapy [a]	165 (81.7)	406 (80.6)	0.69
CPAP [a]	85 (42.1)	259 (51.4)	0.03
Duration of CPAP (d)[b]	5.2±0.7	5.4±1.4	0.05
Mechanical ventilation [a]	154 (76.2)	331 (65.7)	0.006
Maximum PIP [b]	22.6±1.5	20.1±0.7	<0.001
Duration of mechanical ventilation (d)[b]	19.3±0.9	13.3±1.1	<0.001
Duration of oxygen therapy (d)[b]	45.6±9.1	19.7±1.2	<0.001
Maximum FiO_2[a]:			
< 0.60	14 (6.9)	138 (31.3)	
≥0.60	188 (93.1)	366 (68.7)	0.001
Caffeine [a]	92 (45.5)	279 (55.4)	0.02

[a] Number (percent)

[b] Values are mean ±SD

CPAP; continuous positive airway pressure, PIP; peak inspiratory pressure, FiO_2; fraction of inspired oxygen $p < 0.05$; significant

Table 4: Characteristics of preterm survivors according to the severity of CLD

Characteristics	Mild CLD (n=93)	Moderate CLD (n=58)	Severe CLD (n=43)	*P* value
GA (wk)[a]	28.1±1.9	27.9±1.9	27.2±0.1	0.02
BW (g)[a]	960±65	953±45	932±33	0.01
Maximum PIP[a]	21.7±1.9	21.9±0.9	22.7±0.8	0.001
Duration of mechanical ventilation (d)[a]	18.1±0.7	19.2±0.9	19.6±0.6	0.000
Duration of oxygen therapy (d)[a]	44.9±5.2	45.2±6.1	45.4±4.9	0.87

[a] Values are mean +SD
GA; gestational age, BW; birth weight, PIP; peak inspiratory pressure
$p<0.05$; significant

Table 5: Univariate analysis of variables significantly associated with chronic lung disease of prematurity (CLD)

Variables	OR (95% CI)	*P* value
GA	0.81 (0.64-1.15)	<0.01
BW	31.9 (22.9-57.0)	<0.01
Chorioamnionitis	1.8 (1.05-3.09)	0.03
Apgar score at 1 min	0.31 (0.07-0.32)	0.001
Pneumothorax	2.0 (1.08-3.72)	0.03
IVH	2.1 (1.06-3.95)	0.03
CPAP	0.69 (0.49-0.97)	0.04
Mechanical ventilation	1.68 (1.14-2.46)	<0.01
Maximum PIP	2.3 (2.79-2.4)	<0.01
Duration of mechanical ventilation (d)	5.3 (6.17-5.82)	<0.001
Duration of oxygen therapy (d)	30.5 (35.3-33.4)	<0.001
Maximum FiO_2		
< 0.60	0.15 (0.08-0.28)	<0.001
≥0.60		
Caffeine	0.69 (0.49-0.97)	0.03
Frequent blood transfusion	0.44 (0.40-0.57)	<0.001

GA; gestational age, BW; birth weight, IVH; intraventricular hemorrhage, CPAP; continuous positive airway pressure, PIP; peak inspiratory pressure, FiO_2; fraction of inspired oxygen
$p < 0.05$; significant

Table 6: Multivariate analysis for predictors of chronic lung disease of prematurity (CLD)

Variables	OR (95% CI)	*P* value
GA	0.62 (0.43-0.98)	<0.01
BW	20.6 (17.1-29.3)	0.04
Mechanical ventilation	1.07 (0.87-1.54)	0.02
Maximum PIP	1.48 (1.44-1.91)	<0.01
Duration of mechanical ventilation (d)	3.56 (4.28-3.75)	<0.001
Maximum FiO_2		
≥0.60	0.11 (0.05-0.19)	0.001
Frequent blood transfusion	0.64 (0.53-0.87)	<0.01

GA; gestational age, BW; birth weight, PIP; peak inspiratory pressure, FiO_2; fraction of inspired oxygen
$p < 0.05$; significant

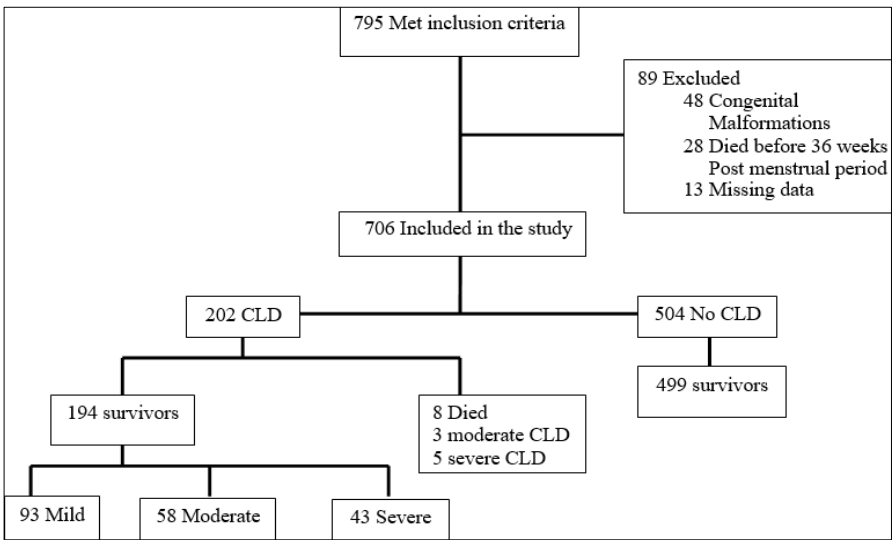

Fig 1: Flow chart of the study population. CLD, chronic lung disease of prematurity

Conclusion

The incidence of BPD in Saudi preterm neonates was 28.6%. The most relevant predictors of CLD were GA, BW, mechanical ventilation, higher PIP, higher FiO_2 use, duration of mechanical ventilation and frequent blood transfusion.

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