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Source / Izvornik: **Journal of Pediatric and Neonatal Individualized Medicine, 2019, 8**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.7363/080129

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:812720

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Download date / Datum preuzimanja: **2025-02-08**

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www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2019;8(1):e080129
doi: 10.7363/080129
Received: 2018 Jul 19; revised: 2018 Oct 21; accepted: 2018 Nov 24; published online: 2019 Apr 30

Original article

Incidence and risk factors for moderate and severe bronchopulmonary dysplasia in very low birth weight infants in two Croatian perinatal regions – a retrospective cohort study

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Abstract

Introduction: Bronchopulmonary dysplasia (BPD) is a significant cause of mortality and morbidity in preterm infants. The incidence of BPD varies widely between centers and is found in 20% to 40% of very low birth weight (VLBW) infants. Our work aimed to examine the incidence and risk factors for moderate and severe BPD in a population of VLBW infants.

Materials and methods: Demographic data, risk factors, incidence and severity of BPD were analyzed for 178 VLBW infants treated in two Croatian perinatal regions (2 level III neonatal units, 2 level II neonatal units and 5 level I neonatal wards) in the period from January 1, 2014 to December 31, 2016.

Results: The rate of BPD was 59.6% (106/178) which is significantly higher than reported earlier. Mild BPD accounted for 65.1% (69/106) and moderate/severe BPD is found in 34.9% (37/106) infants. Among infants with ≤ 28 weeks of gestation, the rate of moderate and severe BPD was 40.5% (30/74). Ultimate risk factors for the development of moderate/severe BPD were late-onset sepsis ($p = 0.03$; OR [95% CI]: 4.76 [1.22-18.5]), and higher initial neonatal risk as expressed by Critical Risk Index for Babies (CRIB) score ($p < 0.001$; OR [95% CI]: 1.73 [1.32-2.29]).

Conclusion: The incidence of moderate and severe BPD in our study group is higher than previously reported, and the majority of affected infants are < 29 weeks of gestation. The factors that had the strongest influence on the development of moderate and severe BPD were a higher initial neonatal risk as expressed by CRIB score and late-onset sepsis.

Keywords

Bronchopulmonary dysplasia, very low birth weight infants, risk factors, incidence, CRIB score, late-onset sepsis.

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How to cite

Kardum D, Filipović Grčić B, Müller A, Dessardo S. Incidence and risk factors for moderate and severe bronchopulmonary dysplasia in very low birth weight infants in two Croatian perinatal regions – a retrospective cohort study. J Pediatr Neonat Individual Med. 2019;8(1):e080129. doi: 10.7363/080129.

Introduction

Since its first description in 1967 by Northway et al. [1], bronchopulmonary dysplasia (BPD) has remained a significant cause of mortality and morbidity in preterm infants [2]. BPD survivors have significant respiratory and quality of life impairment persisting into adulthood [3]. The most severely affected patients may remain symptomatic and have evidence of airway obstruction even as adults [4]. Although lung function improves over time, abnormalities can be detected even in young adults who had severe BPD as infants [4]. BPD has also been associated with poor neurodevelopmental outcomes [5-7].

Since definitions of BPD varied across studies and institutions [8], a workshop was held by the NICHD (National Institute of Child Health and Human Development) in 2000 to clarify the definition of BPD [9]. A severity-based classification was adopted, and BPD is since classified as mild, moderate or severe depending on gestational age at birth and oxygen and respiratory requirements at 36 weeks gestation.

The incidence of BPD varies widely between centers and is found in 20% to 40% of very low birth weight (VLBW) infants and 12% to 13% of preterm infants born before 32 weeks postmenstrual age [10-13].

Development of BPD is multifactorial, and pathogenesis has been linked to a wide variety of prenatal and perinatal risk factors in VLBW neonates [14]. Gestational age is possibly the strongest factor associated with BPD and before 23 weeks' gestation 100% of surviving infants develop BPD [15]. An increased risk of BPD has been associated with prenatal factors such as maternal hypertension, chorioamnionitis, and lack of antenatal steroid therapy as well as with neonatal factors including postdelivery resuscitation, being born small for gestational age [14], higher initial neonatal risk scores [16], the need for mechanical ventilation [17], late-onset sepsis [18-19], and others [14].

Our work aimed to examine the incidence and risk factors for moderate and severe BPD in a population of VLBW infants.

Materials and methods

This retrospective cohort study was performed at General County Hospital Vukovar, General County Hospital Vinkovci, General County Hospital Požega, General County Hospital Slavonski Brod, General County Hospital Našice, University Hospital Osijek, General County Hospital Gospić, General County Hospital Pula, University Hospital Rijeka. The Ethics Committees of all participating hospitals approved the study: GCH Vukovar, 510-05/17; GCH Vinkovci, 01-8246/3/17; GCH Požega, 02-07/52-4/1-1/4-2017; GCH Slavonski Brod, 04/17-93; GCH Našice, 01-537/1-2017; UH Osijek, 19189-3/2017; GCH Gospić, 12-12/17; GCH Pula, 93/53/17-1; UH Rijeka, 003-05/18-1/17.

All life-born neonates in two Croatian perinatal regions (Osijek and Rijeka perinatal regions) were eligible for inclusion in the study if they met the following criteria: they were born between January 1, 2014, and December 31, 2016, in delivery wards in the regions (2 level III neonatal units, 2 level II neonatal units, and 5 level I neonatal wards), their gestational age at birth was ≥ $22^{+0/7}$ weeks, their birth weight was < 1,500 g. 256 infants met the eligibility

criteria. 74 infants died before the primary endpoint and 4 were foreign residents and were transferred to the country of origin for further treatment and data regarding outcomes was unknown. Consequently, the study group included 178 infants.

The primary endpoint for analysis was the incidence of BPD categorized according to severity (mild/moderate/severe). For infants born < 32 weeks gestation the disease was diagnosed at 36 weeks gestational age or at discharge from the hospital, whichever occurred earlier; the diagnostic criteria included supplementary oxygen for at least 28 days, and breathing ambient air (mild BPD), < 30% oxygen (moderate BPD), > 30% oxygen and/or the use of respiratory support (severe BPD). For infants born ≥ 32 weeks gestation the diagnostic criteria included supplementary oxygen for at least 28 days, and breathing ambient air (mild BPD), < 30% oxygen (moderate BPD), > 30% oxygen and/or the use of respiratory support (severe BPD) at 56 postnatal days or discharge, whichever came first.

Gestational age was determined in the following order: (1) an obstetric examination with ultrasonography during the first trimester, (2) obstetric history taking into account the last menstrual period, and (3) a postnatal physical examination of the neonate. Antenatal steroid use was defined as administration of dexamethasone to accelerate fetal maturity with at least 1 dose (incomplete) and at least 4 doses (complete). Chorioamnionitis was defined based on histological findings. Maternal hypertension and late-onset sepsis were defined based on previous studies [20]. Delivery room resuscitation was defined as any endotracheal intubation and/or chest compression and/or fluid boluses and/or any epinephrine administration in the delivery room. Critical Risk Index for Babies (CRIB score) as the initial neonatal risk score was calculated according to the literature [21].

Data were described by using descriptive statistical methods. The ANOVA (Bonferroni corr.) was used to compare the means and medians between two groups, while the Chi-square test and the Fisher's exact test was used to analyze the differences between proportions. Logistic regression was used to analyze the independent factors associated with the risk factor for moderate/severe BPD. The level of significance was set at 0.05. Statistical analysis was performed using MedCalc® Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Results

Clinical characteristics of the study group

The clinical characteristics of the analyzed group are shown in **Tab. 1**. Compared with the infants without BPD, those who developed moderate/severe BPD had lower mean birth weight (913.6 ± 230.4 g vs. 1,262.44 ± 193.9, p < 0.001). Additionally, moderate/severe BPD was associated with a lower gestational age (27 ± 2.0 vs. 31 ± 2.2, p < 0.001), a worse postnatal condition, as expressed by the 5-minute Apgar score (median 7 [5-8] vs 8 [7-10], p = 0.007) and higher initial neonatal risk as expressed by higher CRIB scores (median 5 [2-8] vs 1 [0-1], p < 0.001).

Table 1. Demographic and clinical data of the analyzed group.

Risk factor	BPD			p-value			
	A. No BPD (n = 72)	B. Mild (n = 69)	C. Moderate/ severe (n = 37)	A vs. B vs. C	A vs. B	A vs. C	B vs. C
Birth weight (g), mean (SD)	1,262.44 (193.9)	1,096.41 (202.8)	913.6 (230.4)	< 0.001 [a]	< 0.001 [a]	< 0.001 [a]	0.001 [a]
Gestation (weeks), mean (SD)	31 (2.2)	29 (2)	27 (2)	< 0.001 [a]	< 0.001 [a]	< 0.001 [a]	0.002 [a]
5-min Apgar score, median (IQR)	8 (7-10)	7 (6-10)	7 (5-8)	0.007 [a]	0.13 [a]	0.007 [a]	0.45 [a]
CRIB score, median (IQR)	1 (0-1)	1 (1-2)	5 (2-8)	< 0.001 [a]	0.03 [a]	< 0.001 [a]	< 0.001 [a]
Corticosteriods, n (%)	37 (51)	41 (59)	18 (48)	0.36 [b]	0.39 [c]	> 0.99 [c]	0.38 [c]
Complete course	26 (76)	33 (80)	16 (89)				
Incomplete course	11 (24)	8 (20)	2 (12)				
Singleton/multiple, n/n (% of multiple birth)	54/18 (25)	53/16 (23)	25/12 (32)	0.57 [b]	0.85 [c]	0.49 [c]	0.35 [c]
Chorioamnionitis, n (%)	25 (35)	34 (49)	22 (60)	0.07 [b]	0.09 [c]	0.13 [c]	0.48 [c]
Maternal hypertension, n (%)	17 (24)	16 (23)	8 (24)	> 0.99 [b]	> 0.99 [c]	> 0.99 [c]	> 0.99 [c]

[a] ANOVA (Bonferroni corr.); [b] Chi-square test; [c] Fisher's exact test.
BPD: bronchopulmonary dysplasia; CRIB: Critical Risk Index for Babies.

Incidence and risk factors for moderate/severe bronchopulmonary dysplasia

In the analyzed group, 37 infants (20.8%) developed moderate/severe BPD, while 69 infants (38.8%) had mild BPD. Infants with no BPD accounted for 40.4% (72 infants). As shown in **Fig. 1**, a notable decrease in moderate/severe BPD was observed after 28 weeks of gestation (Fisher's exact test, $p < 0.001$). Therefore, we divided the analyzed group into two subgroups according to gestational age: 24-28 weeks and ≥ 29 weeks completed weeks. There were no survivors at 22 and 23 weeks gestation.

The results of the univariate analysis revealed that in a subset of less-mature infants, the risk factors for moderate/severe BPD were any invasive ventilation during hospitalization, late-onset sepsis and higher initial neonatal risk as expressed by CRIB score. There were no factors reducing the risk of moderate/severe BPD (**Tab. 2**) In the more mature subgroup of infants (born after 29 weeks gestation) the risk factors were later timing of surfactant administration, any invasive ventilation during hospitalization, invasive ventilation > 10 days, late-onset sepsis, presence of hemodynamically significant PDA and higher initial neonatal risk as expressed by CRIB score.

The multivariate logistic regression analysis in two subgroups revealed that in the less mature group the ultimate risk factor for the development of moderate/severe BPD is the higher initial neonatal risk as expressed by CRIB score ($p < 0.001$; OR [95% CI]: 1.61 [1.234-2.10]).

The results of the univariate analysis for all eligible infants revealed that delivery room intubation, any invasive ventilation, invasive ventilation > 10 days, late-onset sepsis, presence of hemodynamically significant PDA and higher initial neonatal risk as expressed by CRIB score were ultimate risk factors for the development of moderate/severe BPD (**Tab. 3**).

The multivariate logistic regression analysis of all infants revealed that the ultimate risk factors for the development of moderate/severe BPD were late-onset sepsis ($p = 0.03$; OR [95% CI]: 4.76 [1.22-18.5)], and higher initial neonatal risk as expressed by CRIB score ($p < 0.001$; OR [95% CI]: 1.73 [1.32-2.29]).

Discussion

Despite significant improvement in survival rates in VLBW neonates in countries with advanced perinatal care, BPD remains one of the main factors influencing neonatal mortality and

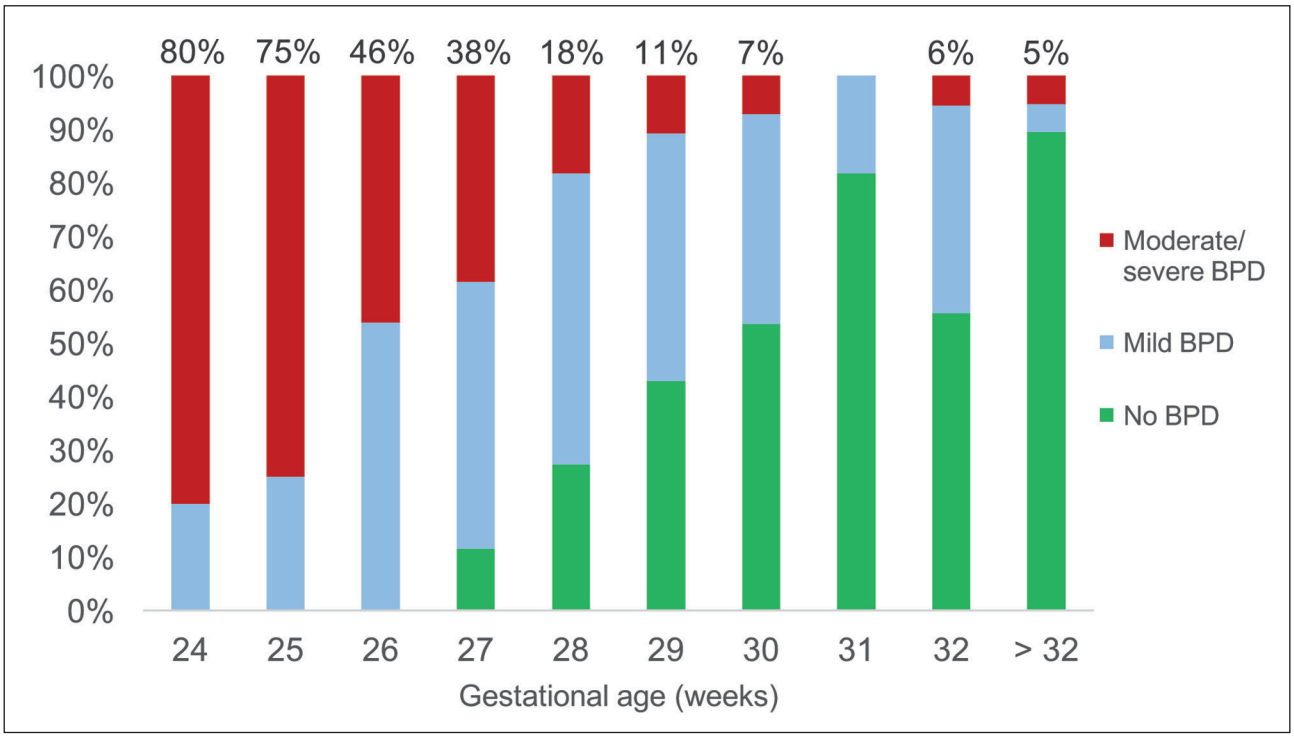

Figure 1. Cumulative histogram of infants with/without bronchopulmonary dysplasia (BPD) in the analyzed group (n = 178). The percentages at the top designate proportion of infants with moderate/severe BPD (red bars).
BPD: bronchopulmonary dysplasia.

Table 2. Univariate logistic regression analysis of risk factors for moderate and severe bronchopulmonary dysplasia (BPD) in two subgroups of premature infants.

Risk factor	24-28 week gestation (n = 74)			≥ 29 week gestation (n = 104)		
	n	p-value	OR (95% CI)	n	p-value	OR (95% CI)
Male gender (yes/no)	34/40	0.84	1.1 (0.43-2.83)	50/54	0.62	0.68 (0.14-3.18)
Corticosteroids, any (no/yes)	32/42	0.11	0.45 (0.17-1.19)	50/55	0.29	2.4 (0.45-13.24)
Corticosteroids, full course (no/yes)	43/31	0.52	0.73 (0.28-1.92)	60/44	0.13	3.7 (0.68-20.1)
Timing of surfactant administration, min (< 30 / > 30)	51/19	0.20	0.47 (0.15-1.50)	42/21	0.04	9.6 (1.004-92.7)
Delivery room intubation (no/yes)	55/19	0.56	1.38 (0.47-4.00)	92/12	0.17	3.5 (0.59-20.3)
Delivery room CPAP (no/yes)	64/10	0.26	0.39 (0.08-1.99)	90/14	> 0.99	#
Invasive ventilation, any (no/yes)	14/60	0.03	9.94 (1.22-80.94)	62/42	0.04	10.2 (1.2-87.9)
Invasive ventilation > 10 days (no/yes)	13/47	> 0.99	#	27/15	0.03	13 (1.35-125.5)
Late-onset sepsis (no/yes)	18/41	0.006	9.3 (1.88-45.6)	44/21	0.04	10.1 (1.1-97.2)
PDA, hemodynamically significant (no/yes)	32/27	0.06	2.8 (0.95-7.98)	58/9	0.02	9.2 (1.5-55.9)
PDA pharmacological clousure (no/yes)	11/16	0.49	0.57 (0.12-2.75)	5/4	0.36	4.0 (0.21-75.65)
CRIB score	-	< 0.001	1.68 (1.32-2.14)	-	0.04	1.38 (1.003-1.89)

OR and 95% confidence intervals for potential risk factors for developing moderate and severe form of bronchopulmonary dysplasia.
#: OR not shown because the confidence interval was too broad (overlapping zero and infinity).
PDA: patent ductus arteriosus; CPAP: continuous positive airway pressure; CRIB: Critical Risk Index for Babies; OR: odds ratios.

Table 3. Univariate logistic regression analysis of risk factors for moderate and severe bronchopulmonary dysplasia (BPD) (all Infants).

Risk factor	p-value	OR (95% CI)
Male gender (yes/no)	0.98	0.99 (0.47-2.09)
Corticosteroids, any (no/yes)	0.63	0.83 (0.39-1.76)
Corticosteroids, full course (no/yes)	0.76	1.12 (0.53-2.39)
Timing of surfactant administration, min (< 30 / > 30)	0.76	0.87 (0.36-2.09)
Delivery room intubation (no/yes)	0.04	2.4 (1.01-5.78)
Delivery room CPAP (no/yes)	0.16	0.34 (0.07-1.54)
Invasive ventilation, any (no/yes)	< 0.001	17.2 (3.96-74.3)
Invasive ventilation > 10 days (no/yes)	< 0.001	40.3 (5.2-312.3)
Late-onset sepsis (no/yes)	< 0.001	13.9 (3.9-49.5)
PDA, hemodynamically significant (no/yes)	< 0.001	5.8 (2.4-14.1)
PDA pharmacological closure (no/yes)	> 0.99	1 (0.26-3.72)
CRIB score	< 0.001	1.75 (1.46-2.1)

BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; CPAP: continuous positive airway pressure; CRIB: Critical Risk Index for Babies; OR: odds ratios.

morbidity even after hospital discharge [22-23]. More interestingly, rates of BPD are not declining in a population of VLBW infants [24]. Kusuda et al. [25] found no change in incidence of BPD in VLBW neonates born over a 5-year period (2003-2008) and the rate remained around 30% when diagnosed at 28 days of life and around 14% when diagnosed at 36 weeks postconceptual age (PCA).

Jo et al. [26] reported that in a study population of 2,386 VLBW infants, 689 were diagnosed with BPD, so the overall BPD rate was 28.9%. Among the 689 BPD VLBW infants, 257 had moderate BPD (37.3%), and 432 had severe BPD (62.7%). Among infants with ≤ 28 weeks of gestation, the overall BPD rate and overall mortality rate were 41.4% and 20%, respectively. These rates are significantly higher than reported in some studies [17].

In our study group, the rate of BPD was 59.6% (106/178), which is significantly higher than reported earlier. Mild BPD accounted for 65.1% (69/106) and moderate/severe BPD is found in 34.9% (37/106) infants. Among infants with ≤ 28 weeks of gestation, the rate of moderate and severe BPD was 40.5% (30/74).

Several factors could influence the overall high rate of BPD in our study group. The rate of any prenatal corticosteroids administration in our population was only 53.9% (96/178) and is significantly lower in studies that report lower rates of BPD [17, 26]. Despite this, in accordance with other studies [27], in our study antenatal corticosteroid administration did not influence the incidence of moderate or severe BPD (OR [95% CI]: 0.83 [0.39-1.76]; p = 0.63).

Secondly, 57.3% (102/178) VLBW neonates in our study population were mechanically ventilated during the hospitalization. In cor-

relation with previous studies, our study found that one of the most critical factors for the development of moderate and severe BPD was invasive ventilation; in the subgroup of more mature infants (> 29 weeks gestation), also the duration of mechanical ventilation > 10 days was a critical factor. This correlation was not found in the subgroup of less mature infants, but this may be due to a large number of them being ventilated for more than 10 days (47/60). Invasive ventilation is one of the critical advances in neonatal care but is associated with the development of BPD due to several mechanisms [28]. For that reason avoidance of invasive ventilation in favor of noninvasive respiratory support is seen as the essential step in preventing neonatal morbidity [28].

Several treatment directions have been studied to reduce the need for mechanical ventilation. Early continuous positive airway pressure (CPAP) and/or INSURE (Intubation, Surfactant administration, and Extubation) procedures are a mainstay in the treatment of respiratory distress syndrome with proposed benefits in terms of better survival and decreased need for mechanical ventilation [29]. The use of CPAP in the delivery room has shown to reduce the risk of BPD, a finding that is supported by extensive multicenter studies [30]. Initial comparisons of CPAP versus invasive ventilation showed a significant reduction of BPD [31] but as noninvasive techniques have been implemented more widely and the invasive ventilation became more "gentle" only a modest benefit of avoiding invasive ventilation was found regarding BPD [24]. Delivery room CPAP was applied to only 13.5% (24/178) infants in our study groups, a finding that could explain a high number of infants eventually mechanically ventilated during their hospitalization.

Other potential strategies include LISA (Less Invasive Surfactant Administration) technique, in which infants receive surfactant treatment during spontaneous breathing via a thin catheter inserted into the trachea by laryngoscopy. Treatment via a LISA technique has recently shown to reduce rates of mechanical ventilation [31], and LISA technique for surfactant delivery resulted in a lesser need for mechanical ventilation in infants with RDS, reduction in the composite outcome of death or BPD at 36 weeks, and BPD at 36 weeks among survivors [29]. A recent meta-analysis [32] showed a significant 34.4% reduction in the risk of BPD with the use of thin catheter compared to INSURE (RR [95% CI]: 0.656 [0.375-1.149]; p = 0.141), although results failed to reach statistical significance.

Intrapartum pharyngeal instillation of surfactant before the first breath may offer the potential benefit of avoiding endotracheal intubation and ventilation, but further studies are needed [33]. Also, novel techniques of laryngeal mask application of surfactant [34] and nebulization of surfactant for avoiding invasive ventilation are considered [35-37]. Other supportive therapies, such as early administration of caffeine citrate [38] and preventive administration of hydrocortisone [39], have shown some benefits in reducing the incidence of BPD. Promising laboratory studies have to lead to early phase clinical trials exploring the feasibility and safety of mesenchymal stromal cells in various pulmonary diseases [40], and first human trials for the treatment of BPD are ongoing [41].

In our study, as in similar studies, we investigated the role of the overall condition of the infants in the first 24 hours of life on the development of BPD [42]. Several illness severity scores have been established to predict mortality and morbidity in neonatal intensive care units [42-44]. In both subgroups of our study group a leading risk factor for moderate/severe BPD was a higher initial neonatal risk as expressed by CRIB score. CRIB categories are significant predictors for oxygen dependency at 42 and 48 weeks of PCA and CRIB is a robust index of initial risk to develop chronic oxygen dependency at 28 days of life and 36 weeks of PCA [16]. Recently, Bruno et al. [45] found that higher CRIB scores correlate with pulmonary hypertension (PH) development in infants with BPD and they speculate that CRIB scores may allow for early categorization of preterm infants with a higher likelihood of developing PH. Our data show that, despite the development of several scores that take into account more parameters than CRIB, CRIB remains a significant predictor of BPD in a specific population of VLBW infants.

In both our study groups, late-onset sepsis was shown to be an ultimate risk factor for the development of moderate/severe BPD (p = 0.03; OR [95% CI]: 4.76 [1.22-18.5]). This finding is consistent with previous studies [18, 19] and with the proposed model of BPD development in which injury to the underdeveloped lung is a major risk factor for the development of BPD [46].

In conclusion, the incidence of moderate and severe BPD in our study group is higher than

previously reported, and the majority of affected infants are < 29 weeks gestation. The factors that had the strongest influence on the development of moderate and severe BPD were a higher initial neonatal risk as expressed by CRIB score and late-onset sepsis. We identified no factors that reduced the risks of moderate and severe BPD. To reduce the risks of development of BPD in our population of VLBW infants, optimal delivery room strategies should be implemented (delivery room CPAP, INSURE, LISA techniques, etc.) with supporting strategies to minimize rates of late-onset sepsis. As Jobe [46] concluded: "The future likely will be refinements of current care strategies rather than any realistic expectation that new therapies will prevent BPD in ELBW infants".

Declaration of interest

The Authors declare no conflict of interest.

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