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A.V. Bolonska,
O.Yu. Sorokina

TREATMENT AND PROPHYLAXIS OF MODERATE AND SEVERE BRONCHOPULMONARY DYSPLASIA IN PREMATURE NEONATES

Dnipro State Medical University
V. Vernadsky str., 9, Dnipro, 49044, Ukraine
Дніпровський державний медичний університет
вул. В. Вернадського, 9, Дніпро, 49044, Україна
e-mail: anna.bolonska@gmail.com

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Ключевые слова: *бронхолегочная дисплазия, недоношенные, новорожденные, респираторная поддержка, профилактика*

Abstract. Treatment and prophylaxis of moderate and severe bronchopulmonary dysplasia in premature neonates. Bolonska A.V., Sorokina O.Yu. *Bronchopulmonary dysplasia in premature neonates leads to physical and mental developmental disorders and behavioral problems and associated with frequent rehospitalizations and long hospital stay. Study objective: to study the predictors of bronchopulmonary dysplasia development in premature neonates in structure of intensive care. Study design: A retrospective cohort analysis was performed in 127 children recruited from two NICU of Dnipro between January 2016 to March 2020. Inclusion criteria: preterm neonates 28-32 gestation weeks with respiratory distress syndrome (RDS). Results demonstrated that every day of mechanical ventilation, supplemental oxygen with FiO_2 more than 30% and cardiac drugs usage increased risk of bronchopulmonary dysplasia development by 15-20%. In conclusion, finding out predictors of bronchopulmonary dysplasia helps to improve and prudently use usual treatment regimens in premature neonates and decrease the frequency of moderate and severe bronchopulmonary dysplasia.*

Реферат. Лікування та профілактика середньотяжких та тяжких форм бронхолегеневої дисплазії в передчасно народжених новонароджених. Болонська А.В., Сорокіна О.Ю. *Розвиток бронхолегеневої дисплазії в передчасно народжених новонароджених призводить до затримки неврологічного та психомоторного розвитку, поведінкових порушень та асоційовано зі збільшенням частоти повторних госпіталізацій та тривалого стаціонарного лікування. Метою цього дослідження стало визначення предикторів розвитку середньотяжкої та тяжкої бронхолегеневої дисплазії в структурі інтенсивної терапії передчасно народжених новонароджених. У дослідження було включено 127 дітей строком гестації 28-32 тижні з діагнозом респіраторного дистрес синдрому з двох неонатальних відділень м. Дніпра в період з 2016 до 2020 р. Результати дослідження виявили, що тривалість знаходження на штучній вентиляції легень, дотація кисню вище 30% у вдихуваній суміші та використання кардіотропів/вазопресорів збільшує ризик розвитку бронхолегеневої дисплазії на 15-20% з кожним днем використання таких методів терапії. Таким чином, виявлення цих факторів ризику в структурі інтенсивної терапії недоношеності дозволяє покращити та зважено провадити деякі підходи в лікуванні таких пацієнтів та зменшити частоту розвитку бронхолегеневої дисплазії середньотяжкого та тяжкого ступеня тяжкості.*

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that leads to disability of premature infants. The incidence of severe forms of BPD in different countries ranges from 17% to 75%, as studies vary significantly depending on gestational age, birth weight, survival rate [3]. According to the current consensus on the treatment of RDS, the incidence of BPD in 2019 was 18% of all patients with RDS [8, 12, 14]. At the same time, it is quite difficult to know how many premature babies actually suffer from respiratory distress syndrome (RDS). Out of 8156 children from Europe, RDS was detected in 80% of children with a gestational age before 28 weeks.

The development of BPD is quite often associated with a high concentration of oxygen in the inhaled mixture, however, the use of devices that control the fluctuations of oxygen in the inhaled mixture did not show significant benefits [10]. Recent studies have focused on mitochondrial oxygen sensitivity and pulse signaling under hypoxia rather than hyperoxia. Incidentally, during oxygen fluctuations on the background of intermittent ventilation under positive pressure, the cells are triggered to exit from a hyperoxic non-hypoxic state in a hypoxia-like reaction, called "hyperoxic-hypoxic paradox" [16].

Considering early postnatal factors, the need for ventilation at birth and the duration of ventilation are among the most important [11]. Early extubation is a priority that determines the need to study all available methods of respiratory support when weaning a patient from a ventilator [29]. For example, extubation can be successful when the mean airway pressure (MAP) level is reduced to 7-8 cm H_2O using traditional mechanical ventilation and at ΔP (pressure difference) at the level of 8-9 cm H_2O on high-frequency mechanical ventilation. Spontaneous respiration tests can be used, however, their effectiveness is debatable [26]. Extubation with a transition to continuous positive airway pressure (CPAP) with a pressure of 7-9 cm H_2O or on non-invasive ventilation with pressure control (NIV PC) may increase the chances of success [7].

A retrospective analysis of infants from the National Institute of Child Health and Human Development (NICHD) has led to a proposal to modify the 2018 NICHD definition [6] to a severity scale of BPD that is based on the use of positive pressure at a 36 weeks' post-conceptual age instead of supplemental oxygen. Infants were classified as "no BPD (no support), grade 1 (nasal cannula ≤2 l/min), grade 2 (nasal cannula >2 l/min or non-invasive positive airway pressure), or grade 3 (invasive mechanical ventilation)". These criteria predicted death or serious respiratory morbidity at 18-26 months corrected age in 81% of infants in the study [6]. Attempts to avoid lung injury in extremely preterm infants have led to recommendations to avoid intubation and ventilation in the first minutes of life and a preference for non-invasive respiratory support [15, 17]. Besides nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV) and high-flow nasal cannulae have become more popular, but the efficacy of these respiratory support methods in reducing the rates of BPD has been modest [19, 20, 21, 33].

NIPPV and NIV PC, these types of noninvasive ventilation are still being studied because there is no single approach to prescribing these types of respiratory support and there is insufficient data on their effects on comorbidities of prematurity [27]. Various studies have examined the impact of various circumstances associated with non-invasive ventilation, such as the interval between extubation and reintubation, on the development of bronchopulmonary dysplasia and mortality [29]. Even extensive reviews of noninvasive ventilation in terms of the impact of different techniques on the development of comorbidities in preterm infants do not give complete answers [17]. And the quality of prevention of reintubation and apnea does not correlate with the development and severity of BPD [18, 22]. The effect of non-invasive ventilation on delayed treatment outcomes and life is insufficient.

There is evidence that adults with BPD in anamnesis vitae have decreased lung function which deteriorates rapidly. It leads to risk of chronic obstructive lung disease development or even death. Thus, the prophylaxis of BPD is one of the main priorities of health care and becomes actual because of potential role in chronic obstructive lung disease pathogenesis [1].

Patients with BPD are more sensitive to respiratory diseases and bronchospasm. Furthermore, BPD can be associated with other healthcare problems as low weight gain, developmental disorders, frequent primary care admissions and rehospitalizations after discharge from NICU [2]. The children with BPD have diminished lung volumes which cause dramatic ventilation-perfusion mismatches even in simple colds [2].

Therefore, the problem of BPD is actual because of its potential role in pathogenesis of chronic lung disease and effective prophylaxis of BPD – one of the main priorities of medicine [1].

The aim of this work was to study the predictors of BPD development in premature neonates in structure of intensive care.

MATERIALS AND METHODS OF RESEARCH

Subjects (n=127) were recruited from two NICU of CE "Dnipropetrovsk Regional Clinical Children's Hospital of Dnipropetrovsk Regional Council" and CE "Dnipropetrovsk Regional Center of Perinatology of Dnipropetrovsk Regional Council" between January 2016 and March 2020. It was retrospective cohort study.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

In accordance to protocol No. 10 17.03.2021 of committee of bioethics of SE "DMA of Ministry of Health of Ukraine" the scientific study was recognized as meeting the generally accepted norms of morality, the requirements of observance of the rights, interests and personal dignity of research participants

All patients received basic treatment according to clinical protocol of treatment of neonates with respiratory disorders No. 484 21/08/2008.

Inclusion criteria were: gestational age 28-32 weeks, diagnosed RDS after delivery, the informed consent signed by parents/caregivers.

Exclusion criteria were: gestational age not less than 28 weeks and no more than 32 weeks, no need in respiratory support, the weight less than 750 g, verified IVH IV stage, congenital malformations which can independently influence respiratory effort.

127 subjects recruited for this study were divided into two groups according to respiratory support features and priority method of non-invasive ventilation (NIV).

54 (42.5%) premature neonates who received triggered noninvasive ventilation with pressure control (NIV PC) during early or/and late neonatal period and restrictive infusion therapy in first week of life.

73 (57.5%) premature neonates who received continuous positive airway pressure ventilation (CPAP) during early or/and late neonatal period and traditional liberal infusion therapy in first week of life.

Patients were observed at different stages of treatment: on admission to the NICU (1st day of life), 3rd day of stay – relative stabilization of vital functions (IVH risk), 7th day – primary weaning from mechanical ventilation (MV) or NIV; 14th day – early complications of prematurity; 28th day – primary BPD suspicion; 56th day of life or on discharge from NICU or 36th week of gestation (diagnosis of BPD).

On primary examination of groups we took into account sex, gestation term (weeks), birth weight (g), length (cm), circumference of the head and thorax (cm). Primary assessment included ultrasound investigation protocol to exclude congenital malformations, as criteria of exclusion from the study, to find out such pathologies as IVH, to assess the hemodynamic significance of patent ductus arteriousus (PDA).

Clinical data dynamically analyzed: temperature (ºC), breathing rate (per min), heart rate (per min), mean arterial pressure (MAP, mmHg), rate of consciousness according to modified Glasgow coma scale, blood saturation (SpO_2, %), diuresis (ml/kg/hr), weight balance (g/day).

Effectiveness evaluation of respiratory support was available due to calculated figures as relation SpO_2/FiO_2 and oxygenation index (OI) [5] and laboratory tests of venous blood gases [4].

Statistics was performed with LibreOffice program and R (version 3.6.3) [24]. The Shapiro-Wilk test was used to assess normality type. Considering 75% of the data had nonnormal distribution, they were presented as median and 25 and 75 percentiles: Me [25%; 75%]. The comparison of qualitative parameters in independent groups was done with Pearson's chi-squared test (χ^2) without Yate's continuity correction. P values <0.05 were considered statistically significant.

Prior to performing the statistics of BPD groups to minimize risk of significant difference we used a method of standardization.

Moreover, the comparison of quantitative values in independent samplings by Kraskell-Wallis criterion was used to evaluate potential confounders of BPD.

To estimate discriminative ability of BPD severity predictors we conducted ROC-analysis (receiver operating characteristics) with calculation of area

under curve (AUC) with 95% CI. *P* values <0.05 were considered statistically significant [33].

RESULTS AND DUSCUSSION

The study data included 67 boys (52.8%) and 60 girls (47.2%) (p=0.27). The birth weight in general data was 1430.0 g [1205, 1765.0], body length was 40.0 cm [35.0; 42.0], gestational age was 30.0 weeks [29.0; 32.0]. There was no significant difference in sex distribution between neonates from NIV PC group: boys 31 (57.4%), girls 23 (42.5%) and in CPAP group: boys 36 (49.3%) and girls 37 (50.6%), p=0.16. Mediana of gestational age in NIV PC group and CPAP group was 31 week [30.0; 32.0] and 30 weeks [28.0; 31.0] respectively. In NIV PC group the mediana of birth weight of neonates was 1710 g [1350; 1900] and in CPAP group this parameter was 1300 g [995; 1485], respectively; body length in NIV PC group of premature neonates was 42 cm [40.2; 44] and in CPAP group body length was significantly less – 36 cm [34; 40.5] cm, p<0.01.

BPD was diagnosed in 48% of premature neonates at 36th week of postconceptual age (PCA) or on discharge from hospital. Mild BPD was verified in 29.1% of all studied infants. Moderate BPD was diagnosed in 11% of general data and in 7.9% of premature neonates severe BPD was diagnosed (Table 1).

The data of neonates of different sex, gestational age, birth weight and body length with verified BPD of all severity stages are represented in Table 1.

Gender structure of patients did not differ significantly in groups with various severity of BPD. But in severe BPD group boys prevailed: 70% in comparison to 30% girls (p=0.27).

There were no significant differences in birth weight, body length, gestational age between BPD severity groups. According to multiple regression model the role of anthropometric and demographic characteristics on BPD development was not defined.

In Table 1 the frequency of BPD development of various severity in premature neonates is presented for NIV PC and CPAP groups separately.

In CPAP group there were more patients without BPD (63,0%) in comparison to NIV PC group, where patients had no BPD in 37.0%, in NIV PC group mild and moderate BPD was recognized more often in 37% and 16,7% cases, respectively. And in CPAP group the frequency of mild BPD was 23.3%, moderate BPD – in 6.8% cases, p=0.03. Nevertheless, the frequency of severe BPD was the same in both group of the study – 5 cases in each group. It meant 9.3% of study population of NIV PC and 6.8% of CPAP group.

Table 1

Demographics of study groups depending on BPD severity

Parameter	Study population (n=127)	No BPD (n=66)	Mild BPD (n=37)	Moderate BPD (n=14)	Severe BPD (n=10)	P Fference
Boys (%)	67 (52.8)	31 (47.0)	23 (62.2)	6 (42.9)	7 (70.0)	0.27
Girls (%)	60 (47.2)	35 (53.0)	14 (37.8)	8 (57.1)	3 (30.0)	
Group NIV PC	54 (42.5)	20 (30.3)	20 (54.1)	9 (64.3)	5 (50.0)	0.03
Group CPAP	73 (57.5)	46 (69.7)	17 (45.9)	5 (35.7)	5 (50.0)	
Body length (cm)	40.0 [35.0;42.0]	39.5 [35.0;42.0]	40.0 [37.0;41.0]	41.0 [37.5;43.8]	40.0 [35.8;41.8]	0.72
Birth weight (g)	1430.0 [1205.0;1765.0]	1440.0 [1200.0;1807.5]	1350.0 [1240.0;1760.0]	1500.0 [1075.0;1730.0]	1375.0 [1270.0;1575.0]	0.91
GA (weeks)	30.0 [29.0;32.0]	30.0 [29.0;32.0]	30.0 [29.0;32.0]	30.0 [30.0;30.0]	30.0 [29.0;31.8]	0.96

Clinical characteristics of the patients depending on BPD verification are presented in Table 2.

Neonates of NIV PC group in 68.4% cases received MV on 1st day of hospital stay and in 29.8% cases still were intubated on 7th day of study. In CPAP group on 1st day 21.6% of infants were mechanically ventilated and on 7th day 25.7% patients still were on mechanical ventilation (MV) (p<0.01).

Subjects from NIV PC group received MV longer than those from CPAP group: 8 [4.5; 18] days and maximum 4,8 [0; 4.8] days respectively (p<0.01).

After weaning from MV, patients from NIV PC group mainly were on triggered NIV PC and its duration was 8 [3.0; 15.0] days and it significantly differed from CPAP group. In CPAP group even if patients received triggered NIV PC its duration was only 2 [0.0; 6.0] days ($p_{1,2}$<0.01). In patients from CPAP group respiratory support in CPAP regimen or bi-level positive airway pressure (BiPAP) was performed and its duration was 5.5 [2; 11.8] days. In NIV PC group CPAP and BiPAP was not used (p<0.01).

We chose multiple risk factors from substantial polymorphism of intensive care approaches in premature neonates and statistically found significant factors (Table 2).

Table 2

Clinical characteristics of study groups depending on BPD verification and severity

Parameter		All patients n=127 (%)	No BPD n=66 (%)	Mild BPD n=37 (%)	Moderate BPD n=14 (%)	Severe BPD n=10 (%)
Duration of MV, days		4.0 [0.0;9.0]	0.0 [0.0;5.0]	6.0 [1.0;11.0]	7 [0.8;11.0]	22.5 [20;41]
Duration of NIV, days		4 [0.0;11.0]	1.0 [0.0;4.0]	8.0 [4.0;16.0]	14 [8.2;16]	1.0 [0.0;13.5]
Suppl. O_2, days		1.0 [0.0;4.0]	1.0 [0.0;3.0]	2.0 [0.0;5.0]	2.5 [1.0;20.2]	4.5 [1.5;8.2]
Cardiac drugs, days		0.0 [0.0;4.0]	0.0 [0.0;2.0]	2.0 [0.0;5.0]	3.5 [0.0;4.8]	3.5 [0.0;9.2]
Salbutamol usage	No	64 (50.4)	55 (83.3)	4 (10.8)	0 (0.0)	5 (50.0)
	Yes	63 (49.6)	11 (16.7)	33 (89.2)	14 (100.0)	5 (50.0)
Inhaled corticosteroids	No	62 (48.8)	54 (81.8)	3 (8.1)	0 (0.0)	5 (50.0)
	Yes	65 (51.2)	12 (18.2)	34 (91.9)	14 (100.0)	5 (50.0)

Note. p<0.01 – the difference is statistically significant between groups.

The statistics was used to analyse the characteristics of respiratory support in infants with different severity of BPD. Among them: dexamethasone for RDS prophylaxis in mothers, SpO_2/FiO_2 ratio and surfactant usage. Also additional factors of intensive care which influenced the respiratory support process were analysed: mean infusion intake, cardiac drugs usage, nebulizer therapy in all BPD groups.

It was estimated that patients' mothers in groups with BPD did not differ in frequency of dexamethasone usage (p=0.23) for RDS prophylaxis. In group with mild BPD it was used in 45.9% of cases, in moderate BPD group – in 50% as well in severe BPD group. There was not found statistically significant difference in surfactant usage between groups (p=0.56). In mild BPD group it was used in 64.9%, in moderate BPD group and severe BPD group – in 71.4% and 70%, respectively.

In mild BPD group (1st day of life) SpO_2/FiO_2 ratio was 282.9 [155.0; 364.0] and did not significantly differ from moderate BPD and severe BPD group – 280,8 [183.8; 329.2] and 205.8 [162.6; 330.0] respectively (p=0.6). These numbers meant that patients from all BPD groups had moderate RDS initially [5]. In comparison, premature neonates without BPD had SpO_2/FiO_2 ratio not significantly different from unhealthy ones – 265.7 [213.3; 352.0].

In severe BPD group the length of MV took 57.7% of time of respiratory support: 22.5 [20.0; 41.0] days, and in moderate BPD group – 7.0 [0.8; 11.0] days. This parameter differed significantly from no BPD group and mild BPD group: 0.0 [0.0; 5.0] days and 6.0 [1.0; 11.0] days, respectively (p<0.01).

MV correlated with the laboratory signs of inflammation during all period of examination, in particular, with the number of leukocytes on 1st, 5th and 7th day of intensive care (R=-0.258; p=0.006), CRP on 3rd, 5th and 7th day (R=0.347; p=0.001, R=0.395; p<0.001 and R=0.436; p<0.001, respectively), the level of platelets on 5th, 7th, 14th day of intensive care (R=-0.368; p<0.001, R=0.450; p<0.001 and R=-0.333; p<0.001, respectively).

In patients with severe BPD the duration of NIV was only 4.5% of the total respiratory support

period – 1 day [0.0; 13.5]. In moderate BPD group patients received NIV significantly longer than in mild BPD group, in fact, by 1.8 times – 14.0 days [8.2; 16.0], p<0.01.

The usage of supplemental oxygen meant gaseous-air mixture, FiO_2>30%. In group without BPD duration of supplemental oxygen usage was 1.0 [0.0;3.0] days and significantly differed from groups with BPD (p<0.01). In mild BPD group the supplemental oxygen was used for 2.0 days [0.0; 5.0]. In moderate and severe BPD groups this parameter increased significantly: 2.5 days [1.0; 20.2] and 4.5 days [1.5; 8.2], respectively.

Mean infusion intake during the first 7 days of life in BPD groups did not differ significantly (p=0.08). But in group without BPD the level of intake was 111.8 [69.4; 117.6] ml/kg/day being by 17.2% higher than in moderate BPD group – 65.0 [52.2; 109.8] ml/kg/day. In group with severe BPD it was 93.3 [50.0; 112.7] ml/kg/day. As well as everyday intake in mild BPD – 89.6 [60.0; 113.2] ml/kg/day.

The prescription of cardiac drugs was dependent on the hemodynamic stability (mean arterial pressure) and cardiac index to support normal level of cerebral autoregulation [30]. We estimated that in groups with moderate BPD cardiac drugs were used for 3.5 days [0.0; 4.8], and in group with severe BPD – 3.5 days [0.0; 9.2], p<0.01.

According to primary statistics in patients from moderate BPD group the nebulizer therapy was the longest and took 53.0 days [30.8; 68.2]. It was by 2.1 times longer than in group without BPD.

We performed univariate logistic regression analysis with the calculation of the odds ratio (OR) to determine the ability of clinical characteristics of patients to predict moderate and severe BPD (Table 3).

Table 3

Predictors of moderate and severe BPD development

Predictor	OR (95% CI)		AUC (95% CI)
Duration of MV, days	**1.07 (1.03-1.12)**	**<0.01**	**0.74 (0.62-0.86)**
Duration of NIV, days	**1.07 (1.02-1.12)**	**0.01**	**0.64 (0.5-0.78)**
Supplemental O_2, days	**1.10 (1.04-1.17)**	**<0.01**	**0.70 (0.58-0.82)**
Cardiac drugs, days	**1.22 (1.08-1.40)**	**<0.01**	**0.65 (0.52-0.78)**
Salbutamol usage	**5.10 (1.88-16.33)**	**<0.01**	**0.68 (0.59-0.78)**
IC usage	**4.71 (1.74-15.08)**	**<0.01**	**0.67 (0.58-0.77)**
MV+ suppl. Oxygen	**1.06 (1.03-1.11)**	**<0.01**	**0.78 (0.66-0.89)**
	1.09 (1.03-1.17)	**<0.01**	

The discriminate characteristics of predictors according to ROC-curves did not differ significantly, although the largest area under the curve was estimated for length of MV (AUC – 0.74 [CI 0.62-0.86]), supplemental O_2 usage (AUC – 0.70 [CI 0.58-0.92]), p<0.01.

Performing ROC-analysis we did not receive significant odd ratios for sex (p=0.88), group of study (NIV PC or CPAP) (p=0.09), birth weight (p=0.77), and gestational age (p=0.8). That is why we demonstrate the AUC only for discriminative signs which had OR with significant p<0.05.

Therefore, patients with moderate and severe BPD were on MV or received supplemental oxygen (FiO_2>30%) significantly for longer period. So, every next day on MV or/and supplemental oxygen (FiO_2>30%) leads to increased likelihood of BPD development by 15% (p=0.01), AUC=0.78 [CI 0.66-0.89]. The prolongation of MV for 1 day increases the risk of moderate and severe BPD development by 7%, AUC=0.74 (95% CI 0.62-0.86), p<0.01. Every day of cardiac drugs usage increases risk of BPD development by 22%. (p=0.01, AUC=0.65 [95% CI 0.52-0.77]).

It was determined that every day of bronchodilators and inhaled corticoids usage increased the risk of severe and moderate BPD development by 3%, AUC=0.70 (95% CI 0.56-0.84) i AUC=0.69 (95% CI 0.55-0.84), respectively. The salbutamol usage increases odd ratio of moderate and severe BPD by 5.1 times, AUC=0.68 (95% CI 0.59-0.78), fluticazone or budesonide usage – by 4.7 times, AUC=0.67 (95% CI 0.58-0.77). So, the prescription of these drugs correlates with the severity of BPD in premature neonates.

Therefore, according to our results, the significant predictors of BPD development were the duration of mechanical ventilation, that of triggered no-invasive ventilation, prolonged cardiac drugs usage, prolonged supplemental O_2 usage and need for salbutamol and inhaled corticoids prescription.

CONCLUSIONS

1. Mothers of premature infants, who then developed severe forms of BPD, were 1.3 times less likely to receive dexamethasone for the prevention of RDS (50%) compared with the group without BPD (65.6%). In patients with severe BPD, the frequency of use of exogenous surfactant (71.4%) did not differ in comparison to children with mild BPD and without it (70.0%), p=0.56.
2. In patients with severe BPD, the duration of mechanical ventilation was 57.7% of the time of all respiratory support, in moderate and mild BPD – 1.9 and 2.2 times less (p<0.01). In the group with severe BPD, the usage of FiO2>30% was probably by 1.8 times longer. An increase in the duration of mechanical ventilation for 1 day increases the chance of development of moderate/severe BPD by 7%, AUC=0.74 (95% CI 0.62-0.86), p<0.01. The prolonged non-invasive pressure control ventilation also increases the chance of development of moderate/severe BPD by 7% with every day usage, AUC=0.64 (95% CI 0.5-0.78).
3. In groups with moderate and severe bronchopulmonary dysplasia vasopressor support lasted for 3.5 days [0.0; 4.8] and 3.5 days [0.0; 9.2], respectively (p<0.01). It was determined that each subsequent day of vasopressor support probably increased the risk of moderate/severe BPD by 22% (p=0.01, AUC=0.65, 95% CI 0.52-0.77).
4. In patients from moderate BPD group the nebulizer therapy was the longest, being 53.0 days [30.8; 68.2]. It was by 2.1 times longer than in group without BPD. The need of salbutamol presciption increases odd ratio of moderate and severe BPD by 5.1 times, AUC=0.68 (95% CI 0.59-0.78), inhaled corticoids usage – by 4.7 times, AUC=0.67 (95% CI 0.58-0.77).

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