EARLY INHALED BUDESONIDE IN EXTREMELY PRETERM INFANTS DECREASES LONG-TERM RESPIRATORY MORBIDITY

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Abstract:	Background:There is no strict correlation between early bronchopulmonary dysplasia and long-term respiratory disease. Early inhaled corticosteroids seem to reduce the incidence of bronchopulmonary dysplasia, but the long-term outcome remains unknown. Research Question:The aim of this study was to evaluate the effect of early inhaled corticosteroids on chronic respiratory morbidity. Methods: Fifty-nine survivors from Prague cohort included in Neonatal European Study of Inhaled Steroids underwent further follow-up comprising of respiratory morbidity monitoring during first two years of life followed by objective lung function testing performed at the age of

	5.9 years (range 5-7 years). Both outcomes were pursued and finalised before un-blinding of budesonide subgroups. Results: Fifty randomised (budesonide vs placebo group, 56 % vs 44 %) survivors were included in the study. Spirometry was successfully performed in 48 children. No statistically significant differences were found in the lung function test (FEF75, FEF50, FEF25 and FEF25-75, FEV1, FVC, FEV1/FVC) although mild trend to the improvement of expiratory flow pattern was observed in the budesonide group (median z-score of FEV1/FVC -0.376 vs -0.983, p=0.13; median z-score of FEF25-75 -1.004 vs -1.458, p=0.13; median z-score of FEF75 -0.527 vs -0.996, p=0.17). Children assigned to budesonide had a significantly lower rate of symptoms of chronic lung disease (34.6% vs 68.2%; P=0.04) than children assigned to placebo. Interpretation: Our study suggests that early inhaled budesonide was associated with the trend to the improvement of functional lung parameters and with a lower rate of symptoms of chronic lung disease within the first two years of life.

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TITLE PAGE

Title: EARLY INHALED BUDESONIDE IN EXTREMELY PRETERM INFANTS DECREASES LONG-TERM RESPIRATORY MORBIDITY

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Key words: inhaled corticosteroids, bronchopulmonary dysplasia, chronic lung disease, spirometry

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ABSTRACT

Background:There is no strict correlation between early bronchopulmonary dysplasia and long-term respiratory disease. Early inhaled corticosteroids seem to reduce the incidence of bronchopulmonary dysplasia, but the long-term outcome remains unknown.

Research Question:The aim of this study was to evaluate the effect of early inhaled corticosteroids on chronic respiratory morbidity.

Methods: Fifty-nine survivors from Prague cohort included in Neonatal European Study of Inhaled Steroids underwent further follow-up comprising of respiratory morbidity monitoring during first two years of life followed by objective lung function testing performed at the age of 5.9 years (range 5-7 years). Both outcomes were pursued and finalised before un-blinding of budesonide subgroups.

Results: Fifty randomised (budesonide vs placebo group, 56 % vs 44 %) survivors were included in the study. Spirometry was successfully performed in 48 children. No statistically significant differences were found in the lung function test (FEF_{75}, FEF_{50}, FEF_{25} and FEF_{25-75}, FEV_1, FVC, FEV_1/FVC) although mild trend to the improvement of expiratory flow pattern was observed in the budesonide group (median z-score of FEV_1/FVC -0.376 vs -0.983, p=0.13; median z-score of FEF_{25-75} -1.004 vs -1.458, p=0.13; median z-score of FEF_{75} -0.527 vs -0.996, p=0.17). Children assigned to budesonide had a significantly lower rate of symptoms of chronic lung disease (34.6% vs 68.2%; P=0.04) than children assigned to placebo.

Interpretation: Our study suggests that early inhaled budesonide was associated with the trend to the improvement of functional lung parameters and with a lower rate of symptoms of chronic lung disease within the first two years of life.

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INTRODUCTION

Preterm birth constitutes an essential risk factor for the adverse respiratory outcome including increased respiratory morbidity, impairment in spirometry and abnormal cross section computed tomography imaging[1-3]. The presence of bronchopulmonary dysplasia (BPD) further increases the risk of long-term respiratory disease. Systemic corticosteroids (CS) before eight days of life appear to decrease the incidence of bronchopulmonary dysplasia and facilitate extubation in high-risk preterm infants[4]. The anti-inflammatory effect of CS may play a crucial role in their favourable impact. However, this benefit may not counterbalance their potential negative effects, such as early complications and adverse long-term neurodevelopmental outcome[4].

There is increasing evidence that early inhaled corticosteroids (ICS) may decrease the incidence of BPD[5, 6] without the adverse effects associated with systemic administration of CS[7]. However, data on the efficacy of ICS on the long-term respiratory outcome are insufficient.

We hypothesised that early ICS would be associated with favourable results of lung function test and with lower respiratory morbidity during early childhood. We thus drew on a multicentre study with early inhalation of budesonide[5] and we conducted a long-term follow-up trial of a Prague cohort enrolled in this study. We assessed spirometry above the age of 4 and chronic respiratory symptoms in the first two years in this cohort.

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MATERIALS AND METHODS

Study design and participants

Our cohort study was designed as a partial extension of the Neonatal European Study of Inhaled Steroids (NEuroSIS, ClinicalTrials.gov, NCT 01035190)[5] that has represented multinational randomized, double-blinded, placebo-controlled trial with early (initiation within 24 hours after birth) inhalation of budesonide by a metered-dose inhaler to extremely preterm infants (gestational age of 23 weeks 0 days to 27 weeks 6 days). In NEuroSIS, two puffs of 200 µg of budesonide each every 12 hours in the first 14 days followed by one puff every 12 hours were administered until the withdrawal of supplemental oxygen and ventilatory support; but no longer than to 32 weeks 0 days). All survivors from the Prague cohort of NEuroSIS were recruited for our follow-up study.

Subjects were excluded for the following reasons: inability to perform spirometry and diagnosis of another chronic respiratory disease. Approval for NEuroSIS study was granted by the Ethics Committee of General University Hospital (1166/10 S-MEK) and written parental consent was obtained for all infants. Follow-up study comprised routine diagnostic and therapeutic process; all parents approved the publication of anonymous data by written consent. We did not involve patients and the public in our study.

Study outcomes

The primary outcome was comprised of spirometry parameters measured in cooperative children above the age of 4 years. Spirometry was performed with the same equipment JAEGER MasterScope Spirometer according to ATS guidelines for pre-schoolers[8] from April 2018 to April 2019. Flow-volume curves were carried out measuring forced vital capacities and expiratory flows. Forced vital capacity (FVC) was chosen to assess a lung volume. Although forced expiratory flow in one second (FEV1) and the ratio of forced expiratory flow

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in one second to forced vital capacity (FEV1/FVC) were reported, the required expiratory flow limitation is usually not achieved at FEV1 in young children[9, 10]. Therefore, forced expiratory flow during mid (25-75%) portion of FVC (FEF25-75) and forced expiratory flow when 75% of FVC has been exhaled (FEF75) were proposed to be more accurate parameters for monitoring of an expiratory flow pattern in young children. The results were presented as Z-scores to adjust for body size, age, and sex using an online calculator (provided by the European Respiratory Society, the Global Lung Function Initiative, 2012[11]).

The secondary outcome was the rate of symptoms of chronic lung disease (CLD symptoms) in the first two years of life (from May 2011 to August 2015) which were assessed according to our predefined criteria by an experienced consultant (table1). We assigned score values to particular CLD symptoms in an effort to test a scoring system for the prediction of respiratory outcome. The respiratory symptoms at rest were marked with the highest value following by the exertional symptoms. Failure to thrive and bronchial obstruction during infection were more dependent on external conditions and were labelled with the lowest value. If at least one criterion was fulfilled, a therapeutic trial with inhaled corticosteroids and bronchodilators was consequently initiated.

Both outcomes were pursued and finalized before unblinding budesonide and placebo subgroups.

Statistical analysis

All tests were set as two-tailed. P-value of less than 0.05 was used as an indicator of statistical significance. Binary data between groups were compared using the Fischer's exact test expressed as p-value, eventually accompanied by risk ratio (RR) with corresponding 95% confidence interval. Ordinal or continuous data without a normal distribution were reported as median and percentiles or range and compared between groups using the Mann-Whitney

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test. Continuous data with normal distribution (checked with the Kolmogorov – Smirnov test) are expressed as mean ± standard deviation and 95% confidence intervals for difference means and compared using the t-test for independent samples. Monotonic relationship between two variables was evaluated by the Spearman's correlation coefficient. All statistical analyses were performed using the software IBM SPSS Statistics, version 21 (21.0.0).

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RESULTS

Study patients

A total of 71 infants has been recruited in the Prague cohort of NEuroSIS. Twelve infants who died at the neonatal intensive care unit were not included; thus fifty-nine children were eligible for our follow-up study. The complete data set was obtained in forty-eight children; two children did not manage to perform spirometry. Nine children were excluded for various reasons (figure 1). The children were further median number of outpatient visit within the first two years was eight.

Table 2 shows comparable demographic and clinical characteristics in both groups.

Respiratory outcomes at NICU did not significantly differ except systemic CS therapy (E-table 3)[12, 13].

Primary outcome

While no statistically significant differences were found in these lung function parameters between the budesonide and the placebo group, Z-scores of several parameters monitoring peripheral bronchial obstruction were nearly two times lower in the budesonide group (table 4).

Secondary outcome

Children assigned to budesonide had a significantly lower rate of CLD symptoms in the first two years than children from the placebo group. This trend was apparent primarily in a subgroup of infants with BPD (table 5). CLD symptoms overlapped with the following prevalence: persistent tachypnea in 27 % of all children, exertional dyspnea in 39.6%, failure to thrive in 18.8%, obstruction during infection in 12.5%.

The most predictive symptom associated with adverse spirometric values was persistent tachypnea that was usually accompanied by exertional dyspnea (table 6). Suggested scoring

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of CLD symptoms (E-table 7) revealed a trend to the correlation between score value and spirometry. However, it did not exceed the predictive value of the presence of persistent tachypnea alone in our cohort (a comparison using a cut off score of 5, E-table 8).

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DISCUSSION

In our follow-up study, it was predicted that early budesonide would result in favourable parameters of spirometry. Even though our results did not reach statistical significance, we observed the auspicious trend to improved Z-scores of several parameters outlining expiratory flow in the budesonide group. Furthermore, we found a significantly lower rate of chronic respiratory symptoms within the first two years of life in children formerly assigned to early inhaled budesonide within NEuroSIS. These results support the hypothesis that early ICS would improve respiratory outcome in ex-preterm children during the first years of life. To our knowledge, this is the first study that examines the long-term impact of ICS on spirometry values and on the incidence of persistent respiratory symptoms in extremely preterm infants.

In the previous study NEuroSIS, Bassler (2015) found a lower rate of bronchopulmonary dysplasia and less frequent reintubation in children assigned to the budesonide compared with the placebo group[5]. Moreover, the effect of different molecules and dosing regimens of various ICS on the incidence of BPD eventually CLD has been already studied. While several trials found no effect of ICS on the incidence of BPD or CLD[14-17], others demonstrate their benefit[18, 19]. However, most studies report favourable short-term impacts of ICS, e.g. reduced mortality, lower prescription of systemic CS, reduced failure to extubate, shorter duration of mechanical ventilation and lower need for oxygen supplementation[15, 16, 20, 21].

Furthermore, the Cochrane metaanalysis conducted by Shah (2017) revealed a reduced incidence of the combined outcome of death or CLD at 36 weeks´ postmenstrual age in all infants and in survivors with early initiation of ICS (within first two weeks of life)[6]. Similarly, the metaanalysis of Shinwell (2016) showed the effect of early or late ICS on the

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reduction of BPD without higher mortality rate[22]. A considerable concern arose from the NEuroSIS study regarding nonsignificant excess in mortality in the budesonide group[5]. Nonetheless, subsequent meta-analyses of seven resp. sixteen trials did not confirm this redoubtable adverse effect[6, 22]. Besides, there was no difference in mortality rate between both groups in our cohort.

Current criteria for the diagnosis of BPD have been based on the level of respiratory support and oxygen dependency at a certain time-point before discharge from the neonatal intensive care unit. Therefore, contemporary BPD represents the short-term condition and has low predictive value for the long-term respiratory outcome[23]. There is little evidence concerning the long-term respiratory impact of early ICS in preterm. Jangaard et al. (2002) found neither difference in the rate of admission to hospital for respiratory problems, nor a change in prescription of inhaled medication in the first three years of life between the children formerly prescribed to early inhaled beclomethasone and placebo group (28 vs 28 children)[14]. By contrast, Yuksel et al. (1992) reported a lower rate of symptoms referred by parents (cough, wheezing), lower use of bronchodilators on-demand and improvement of lung function in 18 infants assigned to inhaled beclomethasone in a randomised controlled trial. Nevertheless, the initiation of ICS in this trial was delayed; the mean age of subjects during the recruitment was 10.5 months (range 3-24 months). Interestingly, the therapeutic success in this trial was defined as an increase in functional residual capacity measured by helium dilution technique[24]. The effect of early systemic budesonide on spirometry was studied by Nixon (2017) in 68 children (8-11 years). A significantly lower rate of abnormal spirometry was observed in the group assigned to budesonide (n=68 vs n=40, p=0.03)[25].

In our study, we proposed unique clinical criteria for the assessment of persistent respiratory disease following prematurity in early childhood. These criteria were derived

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from our clinical experience. To avoid temporary and highly variable clinical parameters such as the one-time value of respiratory rate, we chose conditions that might be markers of prolonged respiratory distress and a substantially limited physiological development or general well-being of the child (Table 1). Persistent tachypnea seemed to represent the most significant predictor of later adverse spirometry. Proposed scoring system with cut-off 5 provided similar predictive value in comparison to persistent tachypnea. Failure to thrive and bronchial obstruction during infection seemed to play a subtle role in the prediction of lung function test.

The main strength of our study includes the fact that potential symptoms of CLD in all participants were assessed by one experienced blinded consultant paediatrician (**DM**) according to predefined clinical criteria.

Interestingly, we observed a noticeable discrepancy between the presence of BPD and low detection of persistent respiratory symptoms in the subgroup of infants with BPD from the budesonide group. This raises the possibility that the impact of early ICS on long-term respiratory outcome might be more substantial than the short-term effect on the diagnosis of BPD.

Spirometry was performed in a single centre by two highly experienced technicians using an identical test protocol, equipment and software. The nonsignificant difference might be related to the limitations of our study.

Firstly, a small total number of subjects with complete data-limited accuracy of statistical analysis. Nevertheless, eligible participants were restricted to the Prague cohort of NEuroSIS, and some of them had to be inevitably excluded. Even though a multicentric follow-up study would enable more accurate statistical evaluation, arranging of comparable clinical assessment and lung function testing with a uniform protocol and equipment

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constitutes a technical, personal and financial challenge. Therefore, we decided to accomplish this partial local research with the potential for a future extension.

Secondly, a treatment initiated after discharge during the first years of the follow-up might represent another confounding factor. We started the therapeutic trial with ICS and betamimetics in case that the persistent respiratory symptoms according to our criteria were observed in an ex-preterm infant. Though there is no consensus on the therapy with ICS in the long-term management of CLD[26] and some authorities warned against the unjustified application of ICS, several studies indicated that a chronic inflammatory process might be persistent to late childhood[27-29]. This leaves open the possibility that a prolonged ICS application after discharge might modify subsequent parameters of lung function test.

Conclusion

Our findings suggest that early ICS might reduce chronic respiratory morbidity in early childhood. The early therapy with inhaled budesonide seems to be a promising tool to improve the long-term prognosis of extremely preterm infants, although we did not prove a significant improvement of spirometry in the treated group. Future studies may confirm the efficacy of ICS in a larger sample, e.g. by extension to a multi-centric follow-up study. Furthermore, a longitudinal assessment of lung function test in these cohorts might make its results more accurate. Further research should be focused on optimisation of dosing regimen, delivery technique and specific effect of different molecules of ICS.

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Contributors: Study concept and design: JT, JS, BZ, RP, and DM. Data acquisition: JT, JS, DM. Analysis and interpretation of data: JT, BZ, RP, DM. Drafting the article: JT, BZ, RP. Critical revision of the manuscript for important intellectual content: JS, BZ, RP and DM. Final approval of the version to be published: JT, JS, BZ, RP and DM. JT and DM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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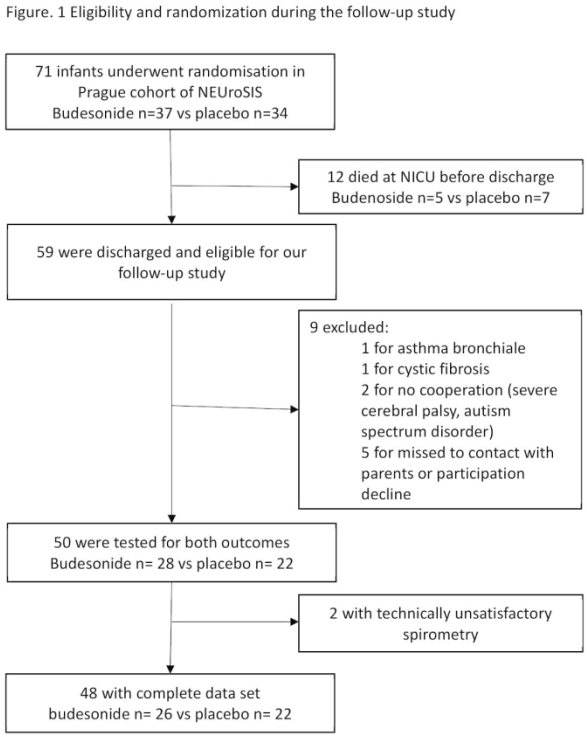

Figure. 1 Eligibility and randomization during the follow-up study

Table 1 Predefined criteria for clinical assessment of CLD symptoms and proposed score value

CLD symptom	Score value
Persistent[a] tachypnea (respiratory rate above 60 breaths/minute)	3
Exertional dyspnea leading to intolerance of the prone position within the first six months	2
Failure to thrive because of increased work of breathing[b]	1
Severe bronchial obstruction during respiratory infections	1

[a]tachypnea repeatedly observed at least two weeks after exclusion of other reasons (infection, other organ system pathology)
[b]failure to gain more than 120 grams per week at least two weeks after exclusion of other reasons (insufficient caloric intake or other organ system pathology such as gastrointestinal, metabolic, neurological, cardiac, endocrine disease)

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Table 2 Base-line characteristics of the infants in the budesonide and placebo group

	BUDESONIDE (N=26)	PLACEBO (N=22)	Statistical significance p-value
Female sex	15 (57.7%)[a]	8 (36.4%)[a]	p=0,16 n.s.
Multiple pregnancy (twins)	7 (26.9%)[a]	4 (18.2%)[a]	p=0.5 n.s.
Antenatal steroids	19 (73.1%)[a]	19 (86.4%)[a]	p=0.31 n.s.
Gestational age (wk)	26 (24-27)[b]	25 (23-27)[b]	p=0.4 n.s.
Birth weight (g)	779 (570-1270)[b]	790 (530-1050)[b]	p=0.7 n.s.
Mortality	5 (13.5%) [a]	7 (20.6%) [a]	p=0.53 n.s.
Age of spirometry (yr)	5-7	5-7	

N-number of children, wk- weeks, yr – years, PPV - positive pressure ventilation, n.s. - not significant

[a]number (percentage), [b]median (range). All children were Caucasians.

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Table 4 Spirometry expressed as mean Z-scores in both groups

	BUDESONIDE (N=26)		PLACEBO (n=22)			
	Mean	SD	Mean	SD	p –value [a]	Difference (mean (95%CI))
FEV1 Z-score	-0.591	0.96	-0.615	1.15	0.94	0.02 (-0.59 to 0.64)
FVC Z-score	-0.286	0.71	0.043	0.77	0.13	-0.33 (-0.76 to 0.10)
FEV1/FVC Z score	-0.376	1.46	-0.983	1.19	0.13	0.61 (-0.17 to 1.39)
FEF 25 – 75 Z score	-1.004	1.06	-1.458	0.95	0.13	0.45 (-0.14 to 1.05)
FEF 75 Z score	-0.527	1.18	-0.996	1.16	0.17	0.47 (-0.21 to 1.15)

SD – standard deviation, CI denotes confidence interval, [a] - independent samples t-test

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Table 5 Respiratory outcomes in first two years

	BUDESONIDE (N=26)	PLACEBO (n=22)	p –value	RR (95%CI)
Oxygen therapy after discharge	None	2 (9.1%)	0.2	
CLD symptoms after discharge in all children	9 (34.6%) [a]	15 (68.2%) [a]	p=0.04	0.508 (0.28-0.93)
CLD symptoms after discharge in subgroup with BPD	8 from 20 (40%)	14 from 18 (77.8%)	P=0.02	0.514 (0.29-0.93)

CLD - chronic lung disease of prematurity, BPD – bronchopulmonary dysplasia, [a] - number (percentage), RR – risk ration, CI denotes confidence interval

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Table 6 Spirometry values in case of presence of particular CLD symptom and its absence

Symptom YES/NO	Tachypnea		Exertional dyspnea		Failure to thrive		Obstruction during infection	
	Difference (mean (95%CI))	p –value[a]	Difference (mean (95%CI))	p –value[a]	Difference (mean (95%CI))	p –value[a]	Difference (mean (95%CI))	p –value[a]
FEV1 Z-score	-0.41 (-1.09 to 0.27)	p=0.23	-0.41 (-1,02 to 0.21)	p=0.19	-0.15 (-0.67 to 0.37)	p=0.56	0.28 (-0.64 to 1.20)	p=0.55
FVC Z-score	-0.13 (-0.62 to 0.36)	p=0.6	-0.11 (-0.55 to 0.34)	p=0.64	-0.26 (-0.82 to 0.30)	p=0.36	0.35 (- 0.30 to 1.01)	p=0.28
FEV1/FVC Z score	-0.37 (-1.26 to 0.52)	p=0.41	-0.22 (-1.03 to 0.60)	p=0.59	0.32 (-0.70 to 1.34)	p=0.53	-0.28 (-1.48 to 0.93)	p=0.65
FEF 25 – 75 Z score	-0.60 (-1.26 to 0.06)	p=0.07	-0.50 (-1.10 to 0.10)	p=0.1	-0.13 (-0.90 to 0.64)	p=0.74	-0.04 (-0.95 to 0.87)	p=0.93
FEF 75 Z score	-0.76 (-1.51 to -0.01)	**p=0.047**	-0.63 (-1.31 to 0.06)	p=0.07	-0.16 (-1.05 to 0.2)	p=0.71	0.02 (- 1.03 to 1.07)	p=0.97

SD – standard deviation, CI denotes confidence interval, [a] - independent samples t-test

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E-Table 3 Respiratory outcomes at NICU

	BUDESONIDE (N=26)	PLACEBO (n=22)	p –value	RR (95%CI)
Diagnosis of BPD (YES)	20 (76.9%)[a]	18 (81.8%)[a]	p=1	0.94 (0.70-1.25)
Moderate and severe BPD	None	3 (13.6%)[a]	p=0.09	
Oxygen therapy at NICU (YES)	22 (84.6%)[a]	20 (90.9%)[a]	p=0.7	0.93 (0.75–1.15)
Ventilatory support (days)	47 (6-70)[b]	50.5 (3-165)[b]	P=0.3	
Systemic corticosteroids at NICU	none	4 (18.2%)[a]	p=0.038	

NICU - neonatal intensive care unit, BPD – bronchopulmonary dysplasia according to definition by Jobe[12] and Walsh[13],[a] - number (percentage), CI denotes confidence interval, [b] - median (range)

E-Table 7 Correlation between proposed score and spirometry

	FEV1 Z-score	FVC Z-score	FEV1/FVC Z score	FEF 25 – 75 Z score	FEF 75 Z score
Correlation Coefficient[a]	-0.165	-0.016	-0.090	-0.260	-0.277
P value[b]	0.264	0.915	0.543	0.074	0.057

[a]Spearman correlation coefficient, [b] - independent samples t-test

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E-Table 8 Comparison of spirometric values (Z-scores) using cut-off score of 5

	score≥ 5 (N=12)		**score < 5 (N=36)**			
	Mean	SD	Mean	SD	p-value[a]	Difference (mean (95%CI))
FEV1 Z-score	-0.94	1.04	-0.49	1.03	p=0.19	-0.46 (-1.15 to 0.24)
FVC Z-score	-0.22	0.87	-0.11	0.72	p=0.64	-0.12 (-0.63 to 0.39)
FEV1/FVC Z score	-0.98	1.43	-0.55	1.34	p=0.35	-0.43 (-1.34 to 0.48)
FEF 25 – 75 Z score	-1.68	0.84	-1.06	1.05	p=0.07	-0.62 (-1.3 to 0.05)
FEF 75 Z score	-1.33	1.07	-0.55	1.17	**p=0.047**	-0.78 (-1.55 to -0.01)

SD – standard deviation, CI denotes confidence interval,[a]- independent samples t-test

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