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Gordana Vilotijević-Dautović^{1,2,†}, Aleksandra Doronjski^{1,2}, Gordana Vijatov-Đurić^{1,2},
Milena Bjelica^{1,2}

**Incidence of bronchopulmonary dysplasia and mortality of very low birth
weight infants in Vojvodina**

Инциденција бронхопулмоналне дисплазије и морталитет новорођенчади
порођајне масе испод 1500 грама у Војводини

¹Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia;

²University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

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†Correspondence to:

Gordana VILOTIJEVIĆ DAUTOVIĆ

Institute of Child and Youth Health Care of Vojvodina, Hajduk Veljkova 10, 21000 Novi Sad, Serbia

Email: gordana.vilotijevic-dautovic@mf.uns.ac.rs

Incidence of bronchopulmonary dysplasia and mortality of very low birth weight infants in Vojvodina

Инциденција бронхопулмоналне дисплазије и морталитет новорођенчади порођајне масе испод 1500 грама у Војводини

SUMMARY

Introduction/Objective The incidence of bronchopulmonary dysplasia (BPD) varies depending on the prematurity rate, definition, and therapy that are applied at a certain center. The average incidence of BPD for very low birth weight infants (VLBW) in developed countries ranges from 4% to 53%. The mortality of VLBW infants is high and represents 50% of the total neonatal and infant mortality. In recent years, the survival limits are shifted towards lower gestations. The aim of our study was to determine the incidence and severity of BPD in VLBW infants in Vojvodina and the overall mortality.

Methods The retrospective study was conducted from January 2006 to December 2011 and included 504 infants with birth weight of <1500 g.

Results In the total population of premature infants, 82.3% survived by the gestational age of 36 weeks. According to the original definition of BPD, as supplemental oxygen use at 28 days of life, BPD had 45.4% of infants. According to the severity based definition 19.4% had mild BPD, 19.8% moderate BPD and 6.5% severe BPD. If BPD is observed as supplemental oxygen use at 36 weeks postmenstrual age, BPD had 26 % of infants.

Conclusion The overall mortality and incidence of BPD in our study are comparable to those in some developed countries and lower compared to underdeveloped countries.

Keywords: bronchopulmonary dysplasia; mortality; incidence; infant, very low birth weight

САЖЕТАК

Увод/Циљ Инциденција бронхопулмоналне дисплазије (БПД) се разликује у односу на стопу прематуритета, као и дефиницију и терапију које се примењују у различитим неонаталним центрима. У различитим земљама инциденција БПД за новорођенчад порођајне масе (ПМ) испод 1500 g варира између 4–53%. Смртност новорођенчади ПМ <1500 g има удео од 50% у укупном морталитету новорођенчади и одојчади. Границе Преживљавања се последњих година померају према нижим гестацијама. Циљ нашег истраживања је утврђивање инциденције и степена тежине БПД, као и морталитета новорођенчади ПМ <1500 g у Војводини.

Метод У периоду од јануара 2006. до децембра 2011. године спроведено је ретроспективно истраживање и обухватило је 504 превремено рођене новорођенчади ПМ <1500 g.

Резултати Од укупног броја превремено рођене новорођенчади ПМ <1500 g преживело је 82.3% до 36. недеље кориговане гестацијске старости (КГС). Посматрајући БПД према дефиницији, што представља оксигенотерапију 28. дана живота, БПД је имало 45.4% новорођенчади. Узимајући у обзир дефиницију која одређује степене тежине, БПД у благом облику је имало 19.44%, средње тежак облик 19.84%, тежак облик 6.15%. Уколико се БПД посматра као зависност од оксигенотерапије 36. недеље КГС, БПД је имало 25.99% новорођенчади.

Закључак Морталитет превремено рођене новорођенчади ПМ <1500 g и учесталост БПД у истраживању које смо спровели су упоредиви са подацима из појединих развијених земаља, а нижи су у поређењу са појединим неразвијеним земљама.

Кључне речи: бронхопулмонална дисплазија; морталитет; инциденција; новорођенче веома мале порођајне масе

INTRODUCTION

When Northway described bronchopulmonary dysplasia (BPD), the gestational age (GA) of infants who had BPD was around 34 weeks and the average birth weight (BW) was 2200g. The mortality rate of those children was 59% [1]. Today, BPD rarely occurs in infants

with BW of more than 1500 g and GA of more than 32 weeks [2]. Since then, new preventive and therapeutic methods were introduced, the most important are: prenatal application of corticosteroids in cases of a risk of premature labor, as well as the surfactant usage and noninvasive ventilation, which enhanced the survival of very low birth weight (VLBW) infants, who are at the greatest risk of having BPD [2,3,4]. For this reason, the incidence of BPD in VLBW infants in recent years mainly stagnates [5].

According to the literature, the incidence of BPD differs in accordance to the rate of prematurity, definition, and therapy that are applied at a certain center [2, 6]. Incidence varies depending on whether BPD is defined according to the original definition - as dependence on oxygen therapy at 28 days of age, according to clinical definition - as dependence on oxygen therapy at 36 weeks postmenstrual age (PMA) or by physiological definition. Differences in incidence also exist depending on which group of infants is taken into account, i.e. which is the upper limit of GA or BW, and whether all infants or only surviving ones are considered. Taking all of differences, the overall average incidence of BPD for VLBW infants in different countries ranges from 4% to 53% [3, 7–11].

According to the data of the neonatal research network of the National Institute for Child Health and Human Development (NICHD) from 1997 to 2002 in VLBW infants at 28 days the BPD incidence ranged from 11% to 41% (on average 25%), at 36 weeks PMA it varied from 10% to 50% (on average 22%) [7]. According to the NICHD's data from 2003 to 2007 in infants with BW of ≤ 1500 g and GA of < 29 weeks the average incidence of BPD according to the severity based BPD definition (Jobe and Bancalari, 2001) was 68% (27% mild, 23% moderate and 18% severe BPD) [5, 12]. Taking into account the clinical definition (at 36 weeks of PMA), the average incidence was 42% (20-89%), and if only surviving infants were considered it was 43%. According to the physiological definition, the average incidence was 40% (15-82%) [5].

The Vermont Oxford Network published that from 2000 to 2009 the incidence of BPD in surviving VLBW infants at 36 weeks PMA recorded a statistically significant decrease (from 27.7 % to 26.3%) [3].

The incidence of BPD in our community has not been determined so far.

There are major variations in different regions in the incidence of BPD in VLBW infants, that indicate that organizational, preventive and therapeutic differences may affect the incidence of BPD, such as: prenatal use of corticosteroids and antibiotics in case of a risk of premature delivery, tocolysis for the purpose of delaying premature labor, application of surfactant, non-invasive mechanical ventilation and other measures [2, 7, 9]. Considering that, in a survey involving infants with GA of <32 weeks from 10 European regions in 2003, the incidence of BPD at 36 weeks PMA ranged from 10.2% to 24.8% [13]. The biggest difference between neonatal care centers was reported in South Korea where the incidence of BPD in infants with BW of <1500 g ranged from 5–50% [14].

The mortality of VLBW infants is high and represents 50% of the total neonatal and infant mortality. The high mortality rate of VLBW infants is due to immaturity of organs and reduced adaptability to extrauterine life [3, 6, 15]. In recent years, after new preventive and therapy strategies were applied, the survival limits are shifted towards lower gestations. The NICHD's data show that the mortality of VLBW infants from 1988 to 1996 was reduced from 26% to 16%. After 1996, mortality rate was decreasing slowly, but the survival rate of the infants with the lowest GAs significantly increased, indicating further progress in perinatal health care [4, 7]. The Vermont Oxford Network's survey showed that from 2000 to 2009 there was a mortality decline of from 14% to 12.4%. The highest drop in mortality was found in the group of infants with the lowest BWs (501–750g), from 41.8% to 36.6%, while in the groups of infants with BW 1001 to 1250 g and 1251 to 1500 g it was constant - about 6% and 3.5% respectively [3].

METHODS

The retrospective study was conducted in the period of 6 years, from January 2006 to December 2011. This study was done in accord with the standards of the institutional Committee on Ethics. The population in study was composed of 504 premature infants with BW of <1500g who were hospitalized in a tertiary Center for newborn and neonatal intensive care at the Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia. In this period, there were 530 VLBW infants. Newborns with congenital heart defects, congenital genetic, metabolic diseases and chromosomopathies, who died for up to 12 hours of life or who did not have all the data needed to be included in the study, were not considered. The incidence and severity of BPD in all live-born and in survived VLBW infants was determined as well as the overall mortality.

RESULTS

Gestational age and birth weight of infants

The average birth weight was 1125.6 ± 280.9 g. Out of the total number of infants ($n = 504$), 32% ($n = 157$) had BW of ≤ 1000 g and 68% ($n = 347$) had BW of > 1000 g (Table 1).

The average GA was 28.78 ± 3.01 weeks. Analyzing by subgroups, the highest number of infants was born at GA of ≤ 32 weeks, 92.7% ($n = 467$), the remaining 7.3% ($n = 37$) was born at GA of 33 to 36 weeks (Table 2).

Incidence of bronchopulmonary dysplasia

According to the definition that takes into account severity of BPD (15), 45.4% ($n = 229$) had BPD, 19.4% had mild BPD, 19.8% moderate BPD and 6.5% severe BPD (Table 3).

If only infants who survived by PMA of 36 weeks are considered, according to the same definition, results are different (Table 4).

Incidences of BPD according to the traditional clinical definition and according to the original definition are shown in Table 4.

All infants with BPD had GA of ≤ 32 weeks. All survived infants with GA of ≤ 24 weeks had BPD. Among the survivors with GA of ≤ 28 weeks 84% had BPD. All infants with GA of < 23 weeks died before the BPD was diagnosed. Moderate BPD most often occurred in all survived GAs, the frequency of mild BPD was gradually increasing with the rise of GA, while the incidence of severe BPD was more frequent in lower GAs (Table 5).

Out of the total number of infants with BW of ≤ 1000 g ($n = 157$), 45.2% (71/157) had BPD at 28 days. Out of the total number of survivors with BW of ≤ 1000 g ($n = 89$), 80% (71/89) had BPD. In infants with BW of > 1000 g ($n = 347$) 45.5% (158/347) had BPD at 28 days and 48.5% (158/326) of surviving ones (Table 6). Out of the total number of infants with BW of ≤ 1000 g 30.6% had BPD at 36 weeks PMA, in case of BW of > 1000 g incidence of BPD was 23.9%.

Mortality

In the total population of premature VLBW infants ($n = 504$) 415 (82.3%) survived by GA of 36 weeks. Out of the total number of deaths ($n = 89$), most occurred during the first week of life ($n = 59$, 66.4%). By 28 days of age 82 infants died (92.1%), from 28 days to 36 weeks PMA, the remaining 8 (8.9%) died. Out of the total number of deaths ($n = 89$), 89% ($n = 79$) occurred in infants with GA of ≤ 28 weeks. All infants GA of < 23 weeks died (100%). Out of the total number of infants with GA of ≤ 28 weeks ($n = 220$), 35.9% ($n = 79$) died as well as 83.78% ($n = 31$) of infants with GA of ≤ 24 weeks. No newborn with GA of more than 33 weeks died (Table 5).

Among infants with BW of >1000 g the mortality rate was low, 6% died. Out of the total number of infants with BW of \leq 1000 g 43% died, with BW of 700-1000g 30% died and among those with BW of \leq 700g 73% died (Table 6).

DISCUSSION

Incidence of bronchopulmonary dysplasia

The results obtained by our study are the first results on the incidence of bronchopulmonary dysplasia in Vojvodina Province, Serbia, on a representative sample of 504 VLBW infants. Since different definitions of BPD are applied in different neonatal centers and published studies, for the purpose of easier comparison, our results concerning incidence are presented in relation to 2 definitions:

- a) According to definition that takes into account the severity of the disease (supplemental oxygen use at 28 days of age, assessment of severity at 36 weeks PMA)
- b) According to the original definition of BPD (supplemental oxygen use at 28 days of age) [2, 10, 12]. These results are shown in Table 3 and Table 4.

According to the literature, the incidence of BPD is variable, but similar in tertiary and secondary healthcare institutions in countries of Western Europe and the United States [2,6].

Our results were first compared to those studies in which the same group of infants was included (BW of less than 1500 g). When we observe the latest results of large studies in developed countries, the incidence of BPD in VLBW infants, according to the definition at 36 weeks PMA, in this study is comparable with the results of some centers, while the incidence of BPD, according to the definition at 28 days, is higher in our study. According to the NICHD's study, the incidence of BPD at 28 days varied from 11 to 41% (on average 25%), which is slightly lower than in our study where the incidence was 45.4%. If a definition at 36

weeks PMA was used incidence ranged from 10–50% (on average 22%), in our research it was 26%, which is 4% more than the average incidence in the NICHD's study but lower than the incidence in some centers included in this study[7]. According to the Vermont Oxford Network's data, using definition of BPD at 36 weeks PMA, the incidence of BPD in surviving VLBW infants was 26.2–30.4% [3]. In our study, the incidence of BPD in surviving VLBW infants at 36 weeks PMA was 31.6%, which is slightly higher. Kusuda et al. reported that in Japan the incidence of BPD in VLBW infants at 36 weeks PMA was 28%, which is 3% more than in our study [16].

In comparison with some developed countries, the incidence of BPD in VLBW infants in study we conducted is higher. Klinger et al. reported that the incidence of BPD in surviving VLBW infants in Israel was 13.7% observed at 36 weeks PMA [17]. Defining BPD in the same way, but taking into account all live born VLBW infants, Isayama et al. published that in Canada the incidence was 12.3% and in Japan 14.6% [8]. Compared to the above-mentioned studies, the incidence of BPD in study we carried out is higher by about 17%. Ali et al. published that according to the severity based definition incidence of BPD in surviving VLBW infants in Denmark was 18%, which is 36% lower than in our study [18].

Demirel et al. reported that the incidence of BPD at 28 days in Turkey in surviving VLBW was 52.8%, Kicinki et al. published that in Poland the incidence of BPD at 28 days in surviving VLBW infants with GA of <32 weeks was 52.7%, which is in both cases comparable to our research where the incidence of BPD in surviving infants at 28 days was 54.3% [19,20]. Fernandez et al. reported that in South America (16 centers from Argentina, Chile, Paraguay, Peru and Uruguay) in VLBW infants the incidence of BPD at 36 weeks PMA is 25%, which is the same as in our study [21]. Yen et al. published that in Taiwan in surviving VLBW infants at 36 weeks PMA the incidence of BPD was 34.9%, which is 3.5% higher than in our study [22].

Data on the incidence of BPD in some studies are presented in relation to GAs, BWs or both.

Incidence of bronchopulmonary dysplasia in relation to gestation age

By reducing GA, the incidence of BPD in survived infant increases (Table 5). The results of our study show that BPD occurs in newborns GA of <32 weeks. Taking into account the definition at 36 weeks PMA in the subgroup of newborns with GA of ≤ 32 weeks BPD had 28%, and in subgroup with GA of ≤ 28 weeks 34.5% of newborns. According to the severity based definition in infants with GA of ≤ 32 weeks BPD had 49%, and in infants with GA of ≤ 28 weeks 53.6% (19.1% mild, 23.18% moderate and 11,36% severe). Presented results match the literature's data, which shows that BPD rarely occurs in infants with GA of more than 32 weeks [2]. In the NICHD's study the incidence of BPD is estimated in VLBW infants with GA of <29 weeks and according to the severity based BPD definition it was 68%, while according to the definition of BPD at 36 weeks PMA it was 41% [5]. The incidence of severity based BPD in infants with GA of ≤ 28 weeks in our study is lower by 15%. The differences in incidence exist also in the subgroup of infants with GA of ≤ 24 weeks. Results in our study show that all surviving infants with GA of ≤ 24 weeks had BPD observed at 28 days and 83% at 36 weeks PMA, while all newborns with GA of <23 week died before defining BPD. In the NICHD's study, half of newborns with GA of ≤ 24 weeks survived, 70–80% had BPD at 36 weeks PMA [5]. Handerson Smart et al. wrote that the incidence of BPD at 36 weeks PMA in New Zealand and Australia in surviving infants with GA of <32 week was 22–25% [23]. In our study, it was higher (34.6%).

Incidence of bronchopulmonary dysplasia in relation to birth weight

The results of our study show that the lower the BW was, the higher was the frequency of BPD in survived VLBW infants. In our study in infants with BW of ≤ 1000 g the incidence of BPD at 28 days and at 36 weeks PMA was 45.2% and 30.6% respectively. In infants with BW of >1000 g the incidence was 45.5% and 23.9%. Botet et al. published that the incidence of BPD at 36 weeks PMA in Spain in infants with BW of <1000 g from 1997–2009 increased from 18% to 24%, which is significantly lower than in our study [24]. In our study the incidence of BPD in infants who survived at 28 days and at 36 weeks PMA was: for BW of ≤ 1000 g 80% and 54%, for BW of >1000 g 48% and 25.5%. In study of Botet et al., the incidence of BPD at 36 weeks PMA in surviving infants with BW of <1000 g ranged from 28% to 31% [24]. Klinger et al. reported that in Israel it was 31% [25]. Latini et al. published that in Italy the incidence of BPD at 28 days in surviving infants with BW of <1000 g increased from the period of 1986 to 2002 to the period of 2002 to 2012 for 9% (from 30.5% to 39.3%), while at 36 weeks PMA it increased from 5.5% to 13.1% [26]. These studies reported a lower incidence than in our study. Farstad et al. published results from Norway, where the incidence of BPD at 28 days in surviving infants with BW of <1000 g or GA of <28 weeks was 86% and at 36 weeks PMA 45% [27]. Tommika et al. reported that in Finland it was 49% [28]. In both studies, the incidence of BPD is higher than in study we carried out. According to the NICHD, the incidence of BPD in infants with BW of ≤ 750 g was 66% at 28 days and 36% at 36 weeks PMA, taking into account that in this study half of infants with BW of ≤ 750 g survived [7]. In our study, the incidence of BPD in infants with BW of ≤ 700 g is low (23%), caused by the high mortality rate before making the diagnosis of BPD (73% of infants died), but in survivors with BW of ≤ 700 g the incidence was high - 85% (at 28 days) and 62% (at 36 weeks PMA).

Mortality

In our study, the mortality rate for different BWs and GAs is shown. The survival rate of VLBW infants, as well as subgroups with BW of >1000 g, is comparable to survival rate in developed countries and higher than survival rate in underdeveloped countries. In contrary to that the survival rate of infants with the lowest BWs and GAs in our study is not as high as in developed countries.

The average BW of patients who died in our study was 831 ± 260 . The mortality rate of premature infants with BW of <1500 g was 17.7%, the survival rate was 82.3%. The NICHD published that the average survival rate of infants with BW of ≤ 1500 g in the US was 85% (ranging from 79 to 93%), which is slightly more than in our study [7]. Ballot et al. reported that in South Africa survival rate of infants with BW of <1500 g was 70.5% which is significantly lower than in our study [29].

The survival rate according to the GA and BW categories is shown in Tables 5 and 6.

Mortality in relation to gestation age

According to data from various regions in Europe, the survival rate of infants with GA of <32 weeks in 2003 was 89.5%, ranging from 93.2% to 74.8% between the regions [13]. In our study for infants with GA of <32 weeks it was 81.1%. According to Fellman et al. in Sweden the survival rate of infants with GA of <27 weeks was 70% (9.8% for GA of 22 weeks to 85% for GA of 26 weeks), which is 43% higher than in our study [30]. According to Isayama et al. survival rate of infants with GA of <25 weeks in Canada was 47.7% and in Japan was 72.9%, while in our study it is significantly lower - 16.3% [8].

Mortality in relation to birth weight

Latini et al. reported that in Italy the survival rate of infants with BW of <1000 g in the period from 1986 to 2012 rose from 42.3% to 72.6%, which is comparable to our research (56.7%) [26]. According to NICHD the survival rate of infants with BW of 1000 to 1250 g was 94% and BW of 1250 to 1500 g was 96%, which is almost identical to the survival rate of the same groups of infants in our study (93% and 95%). In the study we carried out, the survival rate of infants with BW of 751 to 1000 g was 87%, BW of 501 to 750 g was 55%, i.e. survival rate in these categories of BWs was 17% and 29% higher than in our study [7]. Ballot et al. reported that in South Africa, survival rate of infants with BW of 1001 to 1500g was 85.8% and BW of <1000 g was 34.9%, which is 8% and 22% lower than in our study [29].

CONCLUSION

The overall mortality and incidence of BPD in VLBW newborns our study are comparable to those in some developed countries and lower compared to underdeveloped countries. However, the incidence of BPD and mortality rate in VLBW newborns in our study is higher in the population of the most immature infants, especially those with BW of <700 g and GA of <25 weeks, compared with the results from developed countries. These differences can be explained by variations in implementation of available preventive prenatal and therapeutic postnatal measures (prenatal use of corticosteroids and antibiotics in case of a risk of premature delivery, application of surfactant, non-invasive mechanical ventilation), along with the incidence of respiratory distress syndrome, neonatal sepsis and other postnatal risk factors that can influence the outcome, especially the incidence of BPD. Prenatal factors are in close relation with the obstetric praxis while all named postnatal factors can be closely

influenced by technical possibilities of neonatal intensive care units, which are better equipped in developed countries.

NOTE

This paper is a part of a doctoral thesis of dr Gordana Vilotijević-Dautović entitled “Predictive model for bronchopulmonary dysplasia in very low birth weight infants”, defended in 2015, at the Faculty of Medicine of Novi Sad.

Conflict of interest: None declared.

Paper accepted

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Table 1. Birth weight of infants

Birth weight	≤500 g	501–700 g	701–1000 g	1001–1250 g	1251–1499 g	< 1500 g
Number of patients (%)	9 (2)	39 (8)	109 (22)	158 (31)	189 (37)	504 (100)

Paper accepted

Table 2. Gestational age of infants

Gestational age	21–22	23–24	25–26	27–28	29–30	31–32	33–34	35–36	< 36
Number of patients (%)	4 (1)	33 (7)	65 (13)	118 (23)	139 (28)	108 (21)	28 (6)	9 (2)	504 (100)

Paper accepted

Table 3. Incidence and severity of BPD (severity-based definition)

Outcome	Number of patients	%
No BPD	186	36.9
Mild BPD	98	19.4
Moderate BPD	100	19.8
Severe BPD	31	6.1
Died	89	17.6
All	504	100.0

* total BPD = 45.4%

BPD – bronchopulmonary dysplasia

Table 4. Incidence of BPD at 28 days of life and at 36 weeks PMA in all studied infants and in surviving ones

Outcome	Number of patients	%
BPD at 28 days	229/504*	45.4
BPD at 36 weeks PMA	131/504*	26.0
BPD in survivors at 28 days	229/422 [†]	54.3
BPD at 36 weeks PMA in survivors to 36 weeks PMA	131/415 [‡]	31.6
BPD at 28 days in survivors to 36 weeks PMA	229/415 [‡]	55.2
Died	89/504	17.7

* all infants

[†]out of the whole number of infants at 28 days of age there were 422 alive (82 infants died)

[‡]out of the whole number of infants at 36 weeks PMA there were 415 alive (89 infants died)

BPD – bronchopulmonary dysplasia; PMA – postmenstrual age

Table 5. Relationship between gestational age in weeks and the outcome in absolute numbers

Outcome	GA 21–22	GA 23–24	GA 25–26	GA 27–28	GA 29–30	GA 31–32	GA 33–34	GA 35–36	GA <36
No BPD	0 (0)	0 (0)	2 (3)	21 (17)	54 (39)	73 (67)	27 (96)	9 (100)	186
BPD	0 (0)	6 (18)	36 (55)	76 (65)	81 (58)	30 (28)	0 (0)	0 (0)	229
Mild BPD	0 (0)	1 (17)	11 (28)	30 (30)	44 (32)	12 (11)	0 (0)	0 (0)	98
Moderate BPD	0 (0)	4 (66)	15 (39)	32 (33)	32 (23)	17 (16)	0 (0)	0 (0)	100
Severe BPD	0 (0)	1 (16)	10 (26)	14 (14)	5 (4)	1 (1)	0 (0)	0 (0)	31
Death	4 (100)	27 (82)	27 (42)	21 (17)	4 (3)	5 (5)	1 (4)	0 (0)	89
All	4	33	65	118	139	108	28	9	504

* Percentages are given in the brackets

GA – gestational age; BPD – bronchopulmonary dysplasia

Table 6. Relationship between birth weight and the outcome in absolute numbers

Outcome	≤ 500 g	501–700 g	701–1000g	1001–1250g	1251–1499g	<1500
No BPD	1 (11)	1 (3)	16 (15)	55 (35)	113 (60)	186 (37)
BPD	2 (22)	9 (23)	60 (55)	91 (58)	67 (35)	229 (45)
Mild BPD	1 (11)	2 (5)	20 (18)	33 (21)	42 (22)	98 (19)
Moderate BPD	1 (11)	4 (10)	30 (28)	44 (28)	21 (11)	100 (20)
Severe BPD	0 (0)	3 (8)	10 (9)	14 (9)	4 (2)	31 (6)
Died	6 (67)	29 (74)	33 (30)	12 (7)	9 (5)	89 (18)
All	9	39	109	158	189	504

*percentages are given in the brackets

BPD – bronchopulmonary dysplasia