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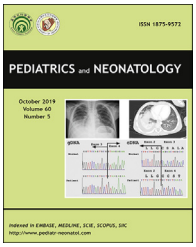

Original Article

Inflammation in the neonatal period and intrauterine growth restriction aggravate bronchopulmonary dysplasia

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Key Words
chronic lung disease;
etiology;
factor;
small-for-gestational-age

Background: To investigate the hematological features of infants with bronchopulmonary dysplasia (BPD) and their relationships with clinical severity.
Methods: This prospective observational study enrolled 73 BPD patients from a total of 331 infants with a birth weight of <1500 g from 2005 to 2013. The clinical severity of BPD was defined by the duration of oxygen supplementation and positive pressure ventilation (PPV) in line with the diagnostic criteria of BPD. The hematological status and cytokine levels were surveyed from blood samples at birth and at 2 and 4 weeks of life.
Results: Thirty-four (46.6%) cases were classified as "moderate-to-severe" BPD. Small-for-gestational-age (SGA) was associated with the severity of BPD (OR: 5.05; 95% CI: 1.45 to 17.2). The CRP level at 2 weeks (partial regression coefficient [rc]: 21.8; 4.01 to 39.7) and the neutrophil count at 4 weeks (0.005; 0.001 to 0.007) were positively correlated with the oxygenation period. The PPV period was found to be correlated with the CRP level at 2 weeks (27.2; 14.9 to 39.5), and the neutrophil count (0.003; 0.001 to 0.004) at 4 weeks.
Conclusion: The aggravation of BPD was associated with both SGA at birth and inflammation during neonatal period.

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1. Introduction

Neonatal bronchopulmonary dysplasia (BPD) was first described by Northway[1] as chronic lung changes in a group of preterm infants who had undergone mechanical ventilation therapy for respiratory distress syndrome (RDS). A variety of therapeutic strategies for BPD have been introduced, including surfactant treatment,[2] postnatal steroid therapy[3,4] and mechanical ventilation techniques such as non-invasive positive pressure ventilation (NIPPV)[5] or high frequency oscillatory ventilation (HFOV).[6] In spite of the changing presentation[7] and diagnostic criteria[8] from "old BPD" to "new BPD of the surfactant era", BPD remains a major complication in preterm very low birth weight infants (VLBWI) who weigh <1500 g at birth. A nationwide neonatal research network in Japan revealed that chronic lung disease, defined as an oxygen requirement at 28 days after birth or 36 weeks of postmenstrual age, affected 33% and 28% of the VLBWIs, respectively.[9]

The pathogenesis of BPD has been recognized as multifactorial, and it includes oxygen toxicity, barotrauma, volutrauma and biotrauma. Biotrauma, especially, is associated with the effects of inflammatory cytokines and chemokines.[10] Prenatal and postnatal inflammation contribute to the development of BPD.[11,12] The cord blood interleukin-6 (IL-6), IL-8, and soluble tumor necrosis factor receptor-1 (sTNFR-1) levels have been shown to be significantly elevated in BPD infants compared with those in controls.[13] The postnatal elevation of the IL-1β, 6, 8 and 10 and interferon gamma (IFN-γ) cytokines and the depression of IL-17 and TNF-β were associated with BPD or death in extremely low birth weight infants (ELBWIs), defined as infants with a birth weight of <1000 g.[14] In contrast, it remains unknown whether clinical and biochemical factors are associated with the aggravation, rather than the pathogenesis, of BPD. We hypothesized that the aggravating factor-specific interventions may be innovative therapeutic strategies for BPD.[8,15]

In this study, we prospectively investigated the hematological features of infants with BPD and their relationship with clinical and radiological severity. The hematological status and cytokine levels were surveyed until 4 weeks of postnatal age. The radiographic severity was determined according to the chest computed tomography (CT) scoring system, as previously reported.[15] Our results could be used to develop the next stage of biotrauma-specific strategies for the BPD infants.

2. Materials and methods

2.1. Patient enrollment

In total, 331 VLBWIs were admitted to the neonatal intensive care units (NICUs) of Kyushu University Hospital between April 2005 and March 2013. Patients who suffered from chromosomal abnormalities, inherited diseases, and/or major constitutional anomalies were excluded from this study. Five neonatologists (MO, KT, HI, JF and MI) were involved in the treatment of 93 (28.1%) BPD patients among all VLBWIs. After obtaining the institutional review board approval for this study protocol (#21−67), informed consent was obtained from the respective caretakers of all patients. The information contained the possible risks and benefits of CT for the assessment of BPD as the patients would be sedated and would receive substantial doses of radiation in comparison to roentgenograms. Twenty of the 93 BPD patients were excluded from the study. Of the twenty patients, nine patients died before discharge. The caretakers of 11 patients declined to participate in the study. Finally, 73 (78.5%) BPD patients (40 male, 33 female) were registered in the study (Fig. 1).

2.2. The clinical information of the infants

The maternal and neonatal records of all of the infants were studied. The information that was collected included the previous obstetric history, the details of the present pregnancy and delivery, morbidity and treatment. The estimated gestational age (GA) was determined as the best obstetric

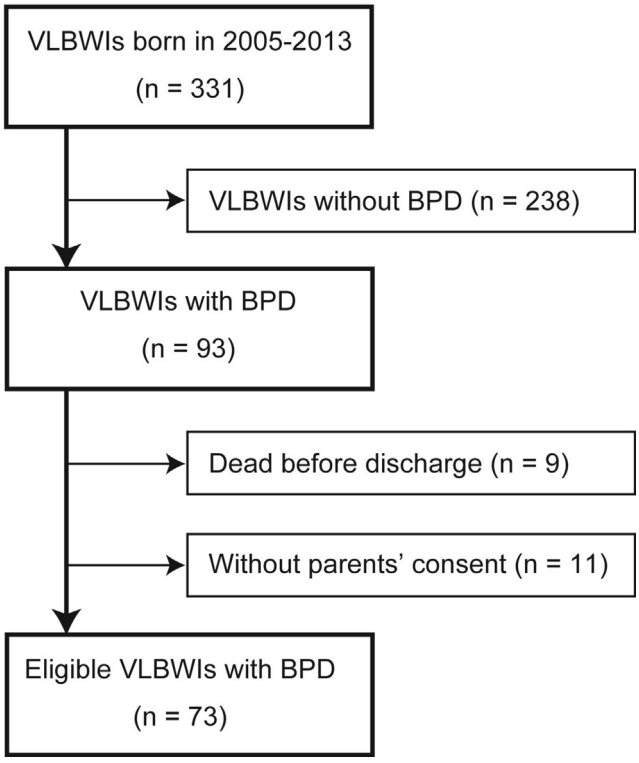

Figure 1 Outline of the patient enrollment.

estimate based on the last menstrual period, standard obstetric parameters and the ultrasonographic findings. The preterm premature rupture of membranes (PPROM) was defined as the spontaneous rupture of fetal membranes occurring before the onset of active labor at less than 37 weeks of gestation. Antenatal steroid therapy was defined as the administration of any corticosteroid to the mothers at 22–34 weeks of gestation to accelerate fetal lung development.[16] Surfactant administration was defined as at least 1 dose of surfactant. Indomethacin treatment was conducted to achieve the closure of patent ductus arteriosus (PDA), which was diagnosed through clinical means or echocardiography. Infants with birth weight (BW) that was more than 10 percentile points below the mean of the standard birth size according to the data of Japanese infants were classified as small-for-gestational-age (SGA).[17] All survivors received brain magnetic resonance imaging (MRI). Intraventricular hemorrhage (IVH) was classified according to the grading scale of Papile et al.[18] Periventricular leukomalacia (PVL) was defined by the observation of cyst formation or ventricular enlargement with irregular walls on MRI.[19] Retinopathy of prematurity (ROP) was defined in accordance with the international classification for ROP.[20] Intestinal perforation was defined as radiological or operative evidence.[21]

2.3. The clinical severity of the BPD infants

The clinical severity of BPD was defined by the duration of oxygen supplementation and positive pressure ventilation (PPV), in line with the diagnostic criteria recommended by the NICHD, NHLBI and ORD Workshops 2001.[8] BPD cases were defined as "mild" if they were "breathing room air at 36 weeks of gestational age or at discharge", "moderate" if they "required less than 30% oxygen at 36 weeks of gestational age or at discharge", and "severe" if they "required more than 30% oxygen and/or PPV at 36 weeks of gestational age or at discharge". The inspired oxygen fraction (FiO_2) to maintain an oxygen saturation (SpO_2) of more than 90% at the beginning of the day's shift was counted, even when it was changed within one day.

2.4. The radiographic severity of the BPD infants

The radiographic severity was determined according to the chest CT scoring system of Ochiai et al.[15] The chest CT findings had nine parameters classified into three categories: (A) hyperexpansion, (B) emphysema and (C) fibrous and/or interstitial abnormalities. Each parameter was scored from 0 to 2 by severity. After adding a parameter to indicate the subjective impression of the overall findings for the three categories above, the range of the scoring system was from 0 to 18, with a higher score reflecting a more severe state. The CT screening was performed when each patient was in a stable condition before discharge. Chest CT scans were obtained with a 3-mm or 5-mm collimation, and images photographed using a lung window were interpreted. Precautionary measures were taken to avoid irradiation above the neck and below the upper abdomen. The gonads of all patients were shielded. Three separate radiologists interpreted and scored the findings without any medical information regarding the patients' backgrounds.

2.5. The biochemical severity of the BPD infants

The hematological status of all of the infants was surveyed from the arterial or venous peripheral blood samples at birth, and at two and four weeks of postnatal age. All tested samples underwent automated interference analyses for hemolysis, icterus and turbidity. The complete blood cell counts (CBC) and differential white blood cell counts were measured using an automated Beckman Coulter Hematology Analyzer (Beckman Coulter Inc., FL, USA). The residual serum was stored at −30 °C until

Table 1 Clinical features of BPD infants (n = 73).

	n (%)
Gender male	40 (54.8)
BW (grams)[a]	642 (267–1458)
GA (weeks)[a]	25.1 (22.7–31.1)
SGA	21 (28.8)
Multiple birth	5 (6.8)
CS	48 (65.8)
PPROM	23 (31.5)
ANS	29 (39.7)
Tracheal intubation at birth	71 (97.3)
Apgar at 1 min (points)[a]	3 (0–9)
Apgar at 5 min (points)[a]	6 (1–9)
Surfactant	70 (95.9)
Postnatal steroid	50 (68.5)
Pulmonary hemorrhage	5 (6.8)
IND	61 (84.7)
Ligation	18 (25.0)
Intestinal perforation	6 (8.2)
IVH ≥ grade III	9 (12.3)
PVL	2 (2.7)
PC	34 (47.2)
Proven sepsis	19 (26.0)
Blood transfusion	55 (75.3)
BPD severity[b]	
Mild	39 (53.4)
Moderate	19 (26.0)
Severe	15 (20.5)
Duration of oxygen[a]	56 (24–320)
Duration of positive pressure[a]	69 (22–194)
CT score[c]	10.0 (2.0–7.3)

[a] Median (range), BPD; bronchopulmonary dysplasia, BW; birth weight, GA; gestational age, SGA; small-for-gestational-age, CS; Caesarean section, PPROM; preterm premature rupture of membranes, ANS; antenatal steroid, IND; indometacin for patent ductus arteriosus, IVH; intraventricular hemorrhage, PVL; periventricular leukomalacia, PC; photocoagulation for retinopathy of prematurity.

[b] Based on the clinical criteria of BPD severity from the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung and Blood Institute (NHLBI) and the Office of Rare Disease (ORD) Workshop 2001.

[c] Based on the chest computed tomography scoring system for BPD by Ochiai et al.

analysis. The concentrations of cytokines (IL-12, TNF, IL-10, IL-6, IL-1β and IL-8) in serum samples were determined by a cytometric bead array (Becton Dickinson, San Jose, CA, USA) and flow cytometry according to the manufacturer's protocol. The detection limit for each cytokine was 4 pg/ml.

2.6. Statistical analysis

All statistical analyses were performed using the JMP^R 11 software program (SAS Institute Inc., Cary, NC, USA). For the non-parametric techniques, categorical variables were analyzed using the chi-squared test, and continuous variables were analyzed using Spearman's rank sum test. We applied a logistic regression analysis for comparison of discrete variables between the clinical factors and the severity of BPD (Table 2), and a multilinear regression analysis to analyze the continuous variables between the biochemical values and the durations of O_2/PPV (Table 3). To avoid type II error in the multivariate analysis, we selected one-tenth dependent variables of the sample size in decreasing order of the OR and correlation coefficient (cc) on univariate analysis in the multiple logistic models. P values of <0.05 were considered to indicate statistical significance.

3. Results

3.1. Clinical features of the BPD infants

We first characterized the clinical features of the BPD infants (n = 73) (Table 1). The median birth weight was 642 g (range: 267–1458 g) and the median gestational age was 25.1 weeks (range: 22.7–31.1 weeks). The median Apgar scores were 3 points (range: 0 to 9 points) at 1 min, and 6 points (range: 0 to 9 points) at 5 min, respectively. Seventy-one (97.3%) of the patients underwent tracheal intubation at birth. Antenatal steroids, surfactants and postnatal steroids were administered to 29 (39.7%), 70 (95.9%), and 50 (68.5%) patients, respectively. Five (6.9%) patients experienced complicated pulmonary hemorrhage and nineteen (26.0%) developed proven sepsis. Sixty-one (84.7%) patients received indomethacin for PDA, and 18 (25.0%) underwent surgical ligation. Thirty-nine (53.4%) of the 73 patients were diagnosed as having "mild BPD". Nineteen (26.0%) and 15 (20.5%) cases were categorized as "moderate" and "severe". The median durations of oxygen therapy and PPV were 56 days (range: 24–320 days) and 69 days (range: 22–194 days). The median radiographic severity score determined by chest CT was 10 points (range: 2.0 to 17.3 points). Thus, the clinical features of BPD

Table 2 Clinical factors associated with the severity of BPD[a].

Variables	"Mild" state of BPD (n = 39)	"Moderate" and "Severe" BPD (n = 34)						
	n (%)	n (%)	Univariate			Multivariate		
			OR	95% CI	p	OR	95% CI	p
Gender male	24 (61.5)	16 (47.1)	0.56	0.22–1.41	0.22			
BW < median; 642 g	13 (33.3)	23 (67.6)	4.18	1.57–11.1	<0.01			
SGA	6 (15.4)	15 (44.1)	4.34	1.44–13.1	<0.01	5.05	1.45–17.5	0.01
GA < median; 25.1 weeks	19 (48.7)	17 (50.0)	1.05	0.42–2.64	0.91			
Multiple births	2 (5.1)	3 (8.8)	1.79	0.28–11.4	0.53			
ANS	16 (41.0)	13 (38.2)	0.89	0.35–2.28	0.81			
PPROM	11 (28.2)	12 (35.3)	1.39	0.51–3.74	0.52			
Apgar <4 points at 5-min.	6 (15.4)	6 (17.6)	1.86	0.58–5.93	0.29			
Proven sepsis	5 (12.8)	14 (41.2)	4.76	1.49–15.2	<0.01	3.56	0.96–13.2	0.06
IVH ≥ grade III	2 (5.1)	7 (20.6)	4.80	0.92–24.9	<0.05	4.98	0.84–29.6	0.08
PVL	1 (2.6)	1 (2.9)	1.15	0.07–19.1	0.92			
IND	33 (84.6)	28 (82.4)	0.71	0.19–2.57	0.60			
Ligation	10 (25.6)	8 (23.5)	0.86	0.29–2.52	0.79			
Postnatal steroid	22 (56.4)	28 (82.4)	3.61	1.22–10.7	0.02			
Pulmonary hemorrhage	2 (5.1)	3 (8.8)	1.79	0.28–11.4	0.53			
Intestinal perforation	2 (5.1)	4 (11.8)	2.46	0.42–14.4	0.30			
PC	14 (35.9)	20 (58.8)	2.75	1.06–7.15	0.04			
Blood transfusion	24 (61.5)	31 (91.2)	6.46	1.68–24.9	<0.01	3.58	0.78–29.6	0.10

OR; odds ratio, CI; confidential intervals, BPD; bronchopulmonary dysplasia, BW; birth weight, GA; gestational age, SGA; small-for-gestational-age, CS; Caesarean section, PPROM; preterm premature rupture of membranes, ANS; antenatal steroid, IND; indometacin for patent ductus arteriosus, IVH; intraventricular hemorrhage, PVL; periventricular leukomalacia, PC; photocoagulation for retinopathy of prematurit.

[a] Based on the clinical criteria of BPD severity from the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung and Blood Institute (NHLBI) and the Office of Rare Disease (ORD) Workshop 2001. Logistic regression analysis was used to investigate the independent variables on the "Moderate" and "Severe" BPD. One-tenth dependent variables of the sample size were selected in decreasing order of the ORs on univariate analysis into the multiple regression models.

Table 3 Biochemical factors associated with the duration of oxygen therapy and positive pressure ventilation (PPV) for BPD.

Variables	Measured value			Duration of oxygenation					Duration of PPV				
				Univariate		Multivariate			Univariate		Multivariate		
	n	median	range	cc	p	rc	95% CI	p	cc	p	rc	95% CI	p
Day 0													
NEUT (/μL)	29	2008	137–21,137	0.19	0.18				0.25	0.08			
CRP (mg/dL)	73	0.01	0.01–6.84	0.14	0.25				0.08	0.50			
IL-6 (pg/ml)	48	11.3	0–1759	−0.02	0.90				0.15	0.30			
IL-8 (pg/ml)	48	53.1	0–1764	0.00	0.99				0.25	0.09			
Day 14													
NEUT (/μL)	65	9444	372–31,502	0.46	<0.01	−0.000	−0.002–0.002	0.93	0.40	<0.01			
CRP (mg/dL)	69	0.04	0.01–4.45	0.32	<0.01	21.8	4.01–39.7	<0.01	0.41	<0.01	27.2	14.9–39.5	<0.01
IL-6 (pg/ml)	33	0	0–200	0.23	0.20				0.49	<0.01	0.15	−0.12–0.41	0.26
IL-8 (pg/ml)	33	33.9	0–287	0.33	0.06				0.40	0.02			
Day 28													
NEUT (/μL)	63	5360	1,214–26,028	0.42	<0.01	0.005	0.001–0.007	<0.01	0.50	<0.01	0.003	0.001–0.004	<0.01
CRP (mg/dL)	69	0.06	0.01–2.24	0.28	0.02	28.3	−5.13–61.9	0.09	0.26	0.03			
IL-6 (pg/ml)	45	0	0–112	0.08	0.62				0.12	0.41			
IL-8 (pg/ml)	45	20.7	0–682	0.29	0.05				0.34	0.02			

cc; correlation coefficient, rc; partial regression coefficient, BPD; bronchopulmonary dysplasia, NEUT; neutrophils, CRP; C-reactive protein, IL-6; interleukin-6, IL-8; interleukin-8, Multiple regression analysis was used to investigate the continuous variables on the duration of oxygen therapy for BPD. One-tenth dependent variables of the sample size were selected in decreasing order of the cc on univariate analysis into the multiple regression models.

infants in this study were consistent with the results in previous reports.[15]

3.2. The clinical factors associated with the severity of BPD

When the perinatal and neonatal characteristics, interventions and morbidities were compared between the "moderate" to "severe" states of BPD (n = 34) and the "mild" state (n = 39), a BW of less than median of 642 g (OR: 4.18; 95% CI: 1.57 to 11.1; p: <0.01), SGA (4.34; 1.44 to 13.1; <0.01), proven sepsis (4.76; 1.49 to 15.2; <0.01), IVH of more than grade III (4.80; 0.92 to 24.9; <0.05), postnatal steroid therapy (3.61; 1.22 to 10.7; 0.02), photocoagulation therapy for ROP (2.75; 1.06 to 7.15; 0.04) and blood transfusion (6.46; 1.68 to 24.9; <0.01) were associated with the severity of BPD in the univariate analysis. SGA was the only significant factor in the multivariate logistic analysis (OR: 5.05; 95% CI: 1.45 to 17.2; p: <0.01) (Table 2).

3.3. The biochemical factors associated with the severity of BPD

We investigated whether the hematological variables of the VLBWIs until 4 weeks of life might be correlated with the duration of oxygen therapy for BPD. When assessed by a univariate analysis, the duration of oxygenation was positively correlated with the neutrophil count (correlation coefficient [cc]: 0.46; p: <0.01) and CRP (cc: 0.32; p: <0.01) level at 2 weeks and the neutrophil count (cc: 0.42; p: <0.01) and CRP (cc: 0.28; p: 0.02) level at 4 weeks. The multilinear regression analysis also indicated that CRP level at 2 weeks (partial regression coefficient [rc]: 21.8; 95% CI: 4.01 to 39.7; p: 0.02) and the neutrophil count at 4 weeks (rc: 0.005, 95% CI: 0.001 to 0.007, p: <0.01) were positively correlated with the duration of oxygen supplementation (Table 3). We further explored whether these biochemical factors might be associated with the duration of PPV in BPD. In the univariate analysis, the duration of PPV was positively correlated with the neutrophil count (cc: 0.42; p: <0.01) and the CRP (cc: 0.41; p: <0.01), IL-6 (cc: 0.49; p: <0.01) and IL-8 (cc: 0.40; p: 0.02) levels at 2 weeks, and duration of PPV was positively correlated with the neutrophil count (cc: 0.50; p: <0.01) and CRP (cc: 0.26; p: 0.03) and IL-8 (cc: 0.34; p: 0.02) levels at 4 weeks. We also verified the correlations of the duration of PPV with serum CRP level at 2 weeks (rc: 27.2; 95% CI: 14.9 to 39.5; p: <0.01) and the neutrophil count (rc: 0.003; 95% CI: 0.001 to 0.004, p: 0.01) at 4 weeks in the multivariate regression analysis (Table 3). The scatter plots between the biochemical factors and the severity of BPD (Fig. 2) also validated those significant correlations. In contrast, the score of radiographic severity on CT was not significantly associated with any of the hematological variables (data not shown). The CT scores, however, had significant correlations between the durations of oxygen therapy (correlation coefficient [cc]: 0.36; p < 0.01) and PPV (cc: 0.32; p < 0.01), respectively.

4. Discussion

Advances in the respiratory management of the premature newborns have seen biochemical injury emphasized as a key etiology of BPD.[7] Some prenatal[11,12] and postnatal[13,14] cytokines and chemokines have been reported to be associated with the onset of BPD. In this study, we investigated whether clinical and biochemical factors are associated

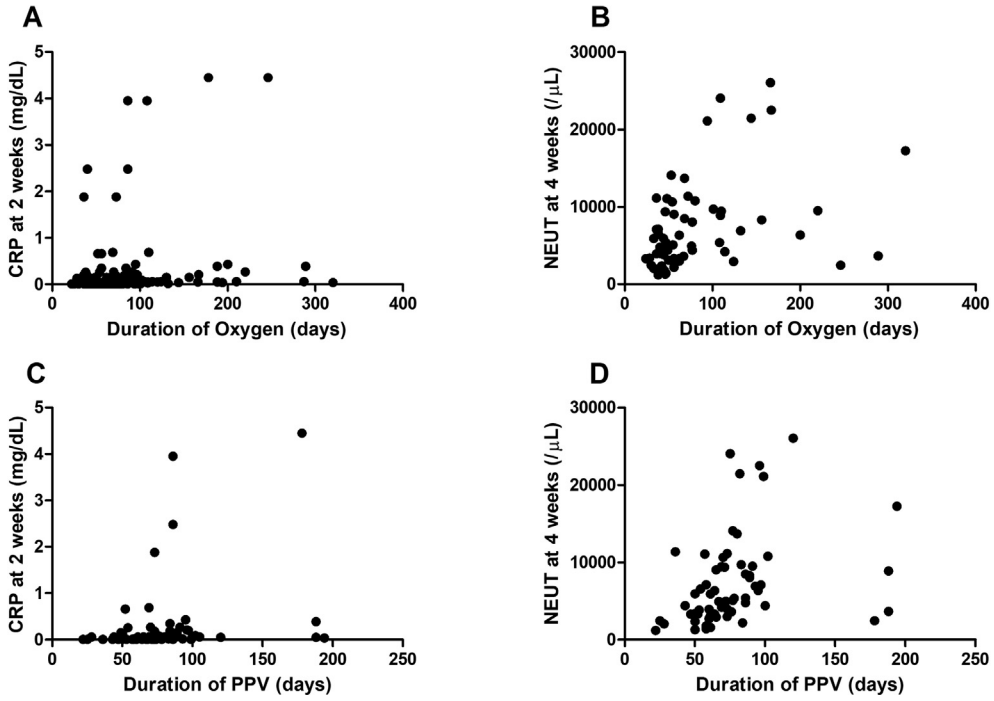

Figure 2 Correlations between the biochemical factors and the severity of BPD. The horizontal axes show the durations of oxygen supplementation (upper column; **A** and **B**) and PPV (lower; **C** and **D**). The serum CRP levels at 2 weeks (left; **A** and **C**) and the neutrophil counts at 4 weeks (right; **B** and **D**) are set on the vertical axes.

with the aggravation of BPD. In fact, the SGA phenotype was associated with the "moderate-to-severe" state of BPD. The CRP level at 2 weeks and the neutrophil count at 4 weeks were positively correlated with the oxygenation period. The correlations of the CRP level at 2 weeks, and the neutrophil count and CRP level at 4 weeks with the duration of PPV were verified by multivariate regression analysis. Our results indicated that SGA and inflammation were aggravating factors for BPD during neonatal period, but not at birth.

Previous studies have revealed numerous factors including lung injuries ranging from early developmental arrest (new BPD) to structural damage of a relatively immature lung (old BPD).[7] A very preterm birth cohort showed that the SGA phenotype was associated with the severity of BPD.[22] Two fetal sheep models revealed that restricting placental and umbilical blood flow resulted in decreased pulmonary alveolar and vessel growth in the fetal lung.[23,24] In addition, the inflammatory responses of SGA infants were deficient in comparison to appropriate-for-gestational-age (AGA) infants.[25] Conversely, SGA infants developed an adequate pro-inflammatory response in spite of the insufficient counter-regulation.[26] Impaired fetal alveolarization and imbalance in the cytokine response might contribute to the development of BPD in SGA infants.

Neutrophils and macrophages are important sources of reactive oxygen species. The inflammatory response and reactive oxygen species contribute to impaired alveolarization, which is characterized by fewer large alveoli and a lower surface area.[27] It was reported that the apoptotic activity of neutrophils in the bronchoalveolar lavage (BAL) samples from BPD infants decreased.[28] Polymorphonuclear leukocytes in cord blood were revealed to have prolonged specific cytotoxic and inflammatory functions.[29] CRP is recognized as a sensitive indicator of inflammation as well as a derivative of adhesion molecules. It was reported that higher serum CRP levels on day 28 were associated with death or development of BPD through the impairment of the pulmonary microcirculation.[30] Neutrophilia and CRP elevation in the neonatal period might affect inflammation, oxygen toxicity and microangiopathy in BPD infants.

There are several possible limitations in this study. One is the measured cytokines from the residual blood samples in a routine hematological survey. Some patients lacked cytokine profiles and could not be evaluated for the association with the severity of BPD. Further studies are needed to evaluate the association between the serum cytokine levels and the severity of BPD accurately. Another is the risk-benefit of the radiographic examination using the chest CT scoring system. Chest CT was performed before discharge when the patients were stable condition. The CT scoring system may have greater objectivity and accuracy than the X-ray in terms of the predischarge assessment of the clinical status as well as the prediction of the prognosis of patients with BPD.[15] On the other hand, a radiation-effective dose from chest CT scanning corresponds up to 200 fold the radiation dosage of the chest X-ray. Further refinements of imaging procedure and other imaging parameter are required to reduce the radiation exposure dose and to clarify the pathophysiology of BPD. We did not use intubation surfactant extubation (INSURE) or less invasive surfactant administration (LISA) methods during the study period. A systematic review and meta-analysis reported that various noninvasive ventilation strategies were effective for preventing BPD.[31] We did not routinely

obtain swabs from the cervix for the diagnosis of intrauterine infection. We should recognize the pattern of intrauterine infection (e.g, bacterial vaginosis, cervicitis, chorioamnionitis, funisitis and proven pathogens) to analyze the pathogenesis of BPD. The other limitation is evidence to compare moderate and severe BPD with mild BPD. The moderate and severe groups were clinically important for the necessity for medical care after hospital discharge. In addition, we were unable to analyze data among the three groups due to small and non-equivalent number of the study population.

5. Conclusion

We concluded that the aggravation of BPD was associated with both SGA at birth and inflammation during neonatal period. The precision medicine that controlled the postnatal inflammation may be anticipated to improve the prognosis of preterm low birth weight infants who suffer from severe BPD.

Conflicts of interest statement

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2018.11.007.