Original Article
Analysis of high-risk factors of preterm infants with mild and moderate bronchopulmonary dysplasia and the value of glucocorticoids in treatment

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Abstract: Objective: To analyze the risk factors of mild and moderate bronchopulmonary dysplasia (BPD) in preterm infants and explore the application value of glucocorticoid treatment. Methods: A total of 118 preterm infants with BPD were divided into the mild group and moderate-severe group according to the severity of the disease. The clinical data of the preterm infants were recorded and risk factors were analyzed. The mild group and moderate-severe group received low-dose corticosteroid treatment. Results: Being small for gestational age, pulmonary hypertension, and duration of continuous positive airway pressure (CPAP) were the independent risk factors for the occurrence of moderate to severe BPD. Consumption of diuretics and fluconazole in the mild group was lower than that in the moderate-severe group, and the mild group had shorter duration of invasive ventilation, CPAP, and oxygen inhalation, hospitalization and antibiotic treatment than the moderate-severe group (*P*<0.05). The mild group had longer head circumference, taller height, and heavier body weight than the moderate-severe group (*P*<0.05) at 6 months after birth. Meanwhile, the mild group also showed more advanced language, cognitive development, and fine and gross motor skills than the moderate-severe group (*P*<0.05). Levels of interleukin-1β and tumor necrosis factor-α in the mild group were lower than those in the moderate-severe group (*P*<0.05). The survival rate during hospitalization in the mild group was 90.57%, and the mortality rate was 9.43%, while the survival rate in the moderate-severe group was 78.46% and the mortality rate was 21.54% (*P*<0.05). Conclusion: There are many risk factors for BPD in premature infants. Glucocorticoid therapy can promote physical development. Earlier use of glucocorticoids will lead to better efficacy.

Keywords: Preterm infants, bronchopulmonary dysplasia, high-risk factors, glucocorticoids

Introduction

Bronchopulmonary dysplasia (BPD) is a severe respiratory disease in preterm infants, and with the continuous progress of medical technology, the survival rate of preterm infants has gradually increased, leading to a corresponding increase in the incidence of BPD [1]. The pathogenesis of BPD is still not fully understood, and it is believed that fibrosis, lung injury, and oxygen dependence are involved in its occurrence and progression [2, 3].

The damage caused by BPD is so severe that respiratory impairment could persist throughout childhood and into adulthood. Compared with mild BPD, moderate-severe BPD will cause more negative outcomes [4]. Clinical research on BPD mainly focuses on the pathogenesis and high-risk factors, but little attention has been paid to the differences in risk factors of varying degrees of BPD in preterm infants. Therefore, the corresponding risk factors of mild to moderate BPD were specifically analyzed in this study. We also further explored the treatment options of neonates with BPD. The most common measures for the prevention of BPD include the use of caffeine and exogenous pulmonary surfactant. However, for preterm infants with confirmed BPD, no standard treatment option is proposed. Glucocorticoids are often prescribed in the treatment of BPD in preterm infants due to their outstanding anti-inflammatory efficacy. In a previous study, glu-

cocorticoids were used in the treatment of preterm infants with BPD, and the inflammatory level was effectively controlled after 1 week [5]. However, its safety was not fully discussed. Some studies have shown that the use of glucocorticoids in the treatment of preterm infants with BPD increase the risk of death [6]. However, some studies have pointed out that glucocorticoids have no direct correlation with death of preterm infants with BPD [7].

This study further analyzed the clinical value of glucocorticoids in the treatment of preterm infants with mild to moderate BPD, and analyzes the difference in curative effect.

Materials and methods

General data

A total of 118 preterm infants with BPD in our hospital were enrolled. According to the diagnostic criteria, 118 premature infants with BPD were divided into the mild group and the moderate-severe group. The mild group had 28 male and 25 female infants, with the average gestational age at birth being (29.31±1.18) weeks, while the moderate-severe group had 35 male and 30 female infants, with the average gestational age at birth being (29.67± 1.34) weeks. Inclusion criteria: infants who were admitted to the Neonatal Intensive Care Unit; with gestational age <32 weeks; with birth weight ≤2 kg; with hospital stay ≥4 weeks; who met BPD diagnostic criteria. Mild criteria [8]: oxygen consumption <28 days, no oxygen support at discharge or 36 weeks of corrected age. Moderate to severe criteria [9]: oxygen consumption ≥28 days, oxygen was required for discharge and mechanical ventilation was required at 36 weeks of corrected age. Their parents signed an informed consent, and the study was approved by ethics committee of our hospital. Exclusion criteria: infants with congenital anomalies; those with congenital heart disease; those with diaphragmatic hernia; those who lacked clinical records; those who were transferred to the surgery department for treatment; those who died during follow-up.

Methods

Both groups received glucocorticoids (Dexamethasone, H41021269, Jiaozuo Furuitang Pharmaceutical Co., Ltd.). Additionally, 0.15 mg/ kg dexamethasone was injected intravenously (qod). The dose was reduced to 0.1 mg/kg after 3 days, to 0.05 mg/kg after another 3 days, and to 0.02 mg/kg for 2 days after another 2 days of treatment.

Observation indicators

Baseline data: (1) Gestational age, gender, birth weight, intrauterine distress, delivery method, and being preterm. (2) Maternal information: age, history of miscarriage, history of eclampsia, prenatal hormone use, prenatal infection, premature rupture of membranes (PROM), amniotic fluid, placental abnormalities, and gestational diabetes mellitus. (3) Diseases or comorbidities of preterm infants: neonatal respiratory distress syndrome, neonatal pneumonia, respiratory failure, sepsis, necrotizing enterocolitis, neonatal ischemic hypoxic encephalopathy, arterial catheter closure, pulmonary hypertension, intraventricular hemorrhage, periventricular leukomalacia (PVL), and intracranial hemorrhage. (4) Hospitalization: duration of invasive ventilation, continuous positive airway pressure (CPAP), oxygen inhalation, and hospitalization costs.

In-hospital treatment: duration of invasive ventilation, CPAP, oxygen inhalation, hospitalization, consumption of antibiotics diuretics, caffeine, fluconazole, and aminophylline following glucocorticoid therapy.

Physical indicators: The head circumference, height, and body weight of premature infants in the mild and moderate-severe groups were measured at 6 months after birth.

Developmental status: the Gesell Developmental Scale [10] was used to evaluate the developmental status of premature infants in the mild and the moderate-severe groups at 6 months after birth. Gesell's research established normative trends for four areas of growth and development, namely (1) motor, (2) adaptive (cognitive), (3) language, and (4) personal-social behavior. The observed behavior pattern is judged with reference to the normal behavior pattern, which is expressed as the developmental age. Compared with the actual age, the development quotient is calculated, and the development quotient (DQ) = development age/actual age * 100. DQ of 85 and above is judged to be a normal nervous system, 75-84 is judged to be a critical level of

Table 1. Analysis of general conditions of the mild group and the moderate-severe group ($\bar{x}$ ± s)/[n (%)]

Data		Mild group (n=53)	Moderate-severe group (n=65)	t/X^2	P
Gender	Male	28 (52.83)	35 (53.85)	0.012	0.912
	Female	25 (47.17)	30 (46.15)		
Gestational age at birth (weeks)		29.31±1.18	29.67±1.34	1.531	0.129
Small for gestational age		2 (9.43)	10 (15.38)	4.309	0.038
Cesarean section rate		13 (24.53)	17 (26.15)	0.041	0.840
Mother >35 years old		5 (9.43)	4 (6.15)	0.446	0.504
Eclampsia or preeclampsia		2 (3.77)	10 (15.38)	4.309	0.038
PNAC		1 (1.89)	8 (12.31)	4.500	0.034
Pulmonary hypertension		1 (1.89)	9 (13.85)	5.384	0.020
ROP		4 (7.55)	14 (21.54)	4.421	0.036
Days of invasive ventilation (d)		2.13±1.05	4.84±1.73	9.997	0.000
CPAP time (d)		16.85±3.64	21.18±4.19	5.919	0.000
Oxygen inhalation time (d)		35.16±5.85	43.89±8.71	6.237	0.000
Antibiotic use time (d)		50.16±15.38	62.18±18.70	3.756	0.000

nervous system damage, and DQ<75 is judged to be a nervous system injury.

Inflammation status: The levels of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in the mild group and the moderate-severe group were measured before and after treatment, and venous blood samples were drawn at two time points. Serum was collected and examined using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) in strict accordance with the kit instructions.

Survival rate: Survival rate and mortality rate of premature infants in the mild and moderate-severe groups during hospitalization were recorded.

Statistical analysis

Statistical analysis was performed with SPSS 23.0. Measurement data ($\bar{x}$ ± s) were compared by independent sample t test. Count data [n (%)] were compared by chi-squared test. Multi-point comparison was analyzed by ANOVA and F test. The figures were illustrated using Graphpad Prism 8. $P<0.05$ was considered statistically significant.

Results

Baseline data

Among the 118 cases of preterm infants with BPD included in this study, 53 were classified as mild and 65 were moderate or severe. There was no difference in the gender ratio, gestational age at birth, cesarean section rate, and ratio of mother's age >35 years in two groups ($P>0.05$). The proportion of being small for gestational age, eclampsia or preeclampsia, parenteral nutrition-related cholestasis (PNAC), pulmonary hypertension, and retinopathy (ROP) in the mild group was lower than those in the moderate-severe group. The mild group also showed shorter duration of invasive ventilation, CPAP, oxygen inhalation and lower consumption of antibiotics than the moderate-severe group ($P<0.05$) (**Table 1**).

Logistic regression analysis of BPD risk factors

Being small for gestational age, eclampsia or preeclampsia, PNAC, pulmonary hypertension, ROP, days of invasive ventilation, CPAP, oxygen inhalation and antibiotic consumption were taken as the independent variables, and moderate to severe BPD was regarded as the dependent variable. Multivariate logistic regression analysis showed that being small for gestational age, pulmonary hypertension, and duration of CPAP were the independent risk factors for moderate to severe BPD (**Table 2**).

Glucocorticoids improve treatment in the hospital

The frequency of diuretics (3.77%) and fluconazole (62.26%) consumption in the mild group were lower than those in the moderate-severe

Table 2. Logistic regression analysis of risk factors affecting the occurrence of moderate to severe BPD

Variable	β	SE	OR	P	95% CI
Small for gestational age	1.345	0.672	3.829	0.041	1.032~14.258
Eclampsia or preeclampsia	1.400	0.816	4.052	0.086	0.835~19.637
PNAC	2.031	0.713	7.458	0.003	1.861~28.734
Pulmonary hypertension	1.683	0.759	5.195	0.038	1.482~23.316
ROP	0.030	0.008	1.016	0.157	0.618~1.062
Days of invasive ventilation	0.062	0.047	1.032	0.182	0.829~1.342
CPAP time	0.035	0.019	1.027	0.041	1.035~1.052
Oxygen inhalation time	1.052	0.369	2.198	0.127	0.528~1.017
Antibiotic use time	0.316	0.021	0.859	0.318	0.135~1.029

group (15.38%, 80.00%) ($P<0.05$). No difference was found in the frequency of caffeine and aminophylline consumption between the two groups ($P>0.05$) (**Table 3**). The mild group had shorter duration of invasive ventilation, CPAP, oxygen inhalation, hospitalization, and lower antibiotic consumption than the moderate-severe group ($P<0.05$) (**Figure 1**).

Glucocorticoids improve physical indicators

At 6 months after birth, the head circumference, height, and body weight in the two groups were measured. The head circumference was (43.02±0.67) cm and height was (68.52±4.19) cm in the mild group, longer than (41.19±0.62) cm and (63.12±3.58) cm in the moderate-severe group. Infants in the mild group weighted (7.58±0.69) kg, which was greater than (6.99±0.65) kg in the moderate-severe group ($P<0.05$) (**Figure 2**).

Glucocorticoids improve developmental status

On the Gesell scale, the developmental status of the preterm infants with BPD in the mild group at 6 months of birth was higher than that of the preterm infants with moderate and severe BPD in the moderate-severe group at 6 months of birth. The scoring results and the differences in the scores were statistically significant ($P<0.05$) (**Figure 3**).

Glucocorticoids reduce inflammation status

There was no significant difference in the levels of inflammatory factors IL-1β and TNF-α in the two groups before treatment ($P>0.05$). IL-1β and TNF-α levels were decreased in both groups after treatment ($P<0.05$), and they were

lower in the mild group than in the moderate-severe group ($P<0.05$) (**Figure 4**).

Glucocorticoids improve survival status

The mild group had 48 cases of premature infants with BPD survived during hospitalization, and the survival rate was 90.57%, which was higher than 78.46% (51 cases) of the moderate-severe group. There were 4 infants who died in the mild group with a mortality rate of 9.43%, which was lower than 21.54% (14 cases) in the moderate-severe group ($P<0.05$) (**Table 4**).

Discussion

Promoted by the continuous development of medical technology, more premature infants can be delivered successfully [11]. Although the survival rate for premature infants has improved over time, they are less fully developed and have an increased risk of complications compared to full-term infants [12]. Statistics found that premature infants born at less than 28 weeks of age are likely to have a 55% chance of developing BPD after birth [13]. A study has shown that the risk of BPD co-occurrence in preterm infants is negatively correlated with gestational age, that is, preterm infants with lower gestational age will have a greater risk of BPD [14].

BPD can prolong the hospitalization time of premature infants, increase the medical cost and affects the prognosis of premature infants [15]. Especially for premature infants with moderate to severe BPD, the risk of respiratory and nervous system abnormalities is very high, and prevention of BPD is a prerequisite for improving the prognosis of premature infants. Determining the risk factors for the occurrence of BPD is an important basis for guiding clinical treatment plans and controlling the occurrence of BPD in preterm infants. In this study, it was found that mild BPD accounted for 44.92% and moderate to severe BPD accounted for 55.08%. This similar proportion suggests that physicians must pay more attention to the severity of BPD in preterm infants. A

Table 3. Treatment data of the mild group and the moderate-severe group after receiving hormone therapy [n (%)]

Grouping	Number of cases	Diuretic	Caffeine	Fluconazole	Aminophylline
Mild group	53	2 (3.77)	5 (9.43)	33 (62.26)	16 (30.19)
Moderate-severe group	65	10 (15.38)	8 (12.31)	52 (80.00)	20 (30.77)
X^2		4.309	0.246	4.559	0.005
P		0.038	0.620	0.033	0.946
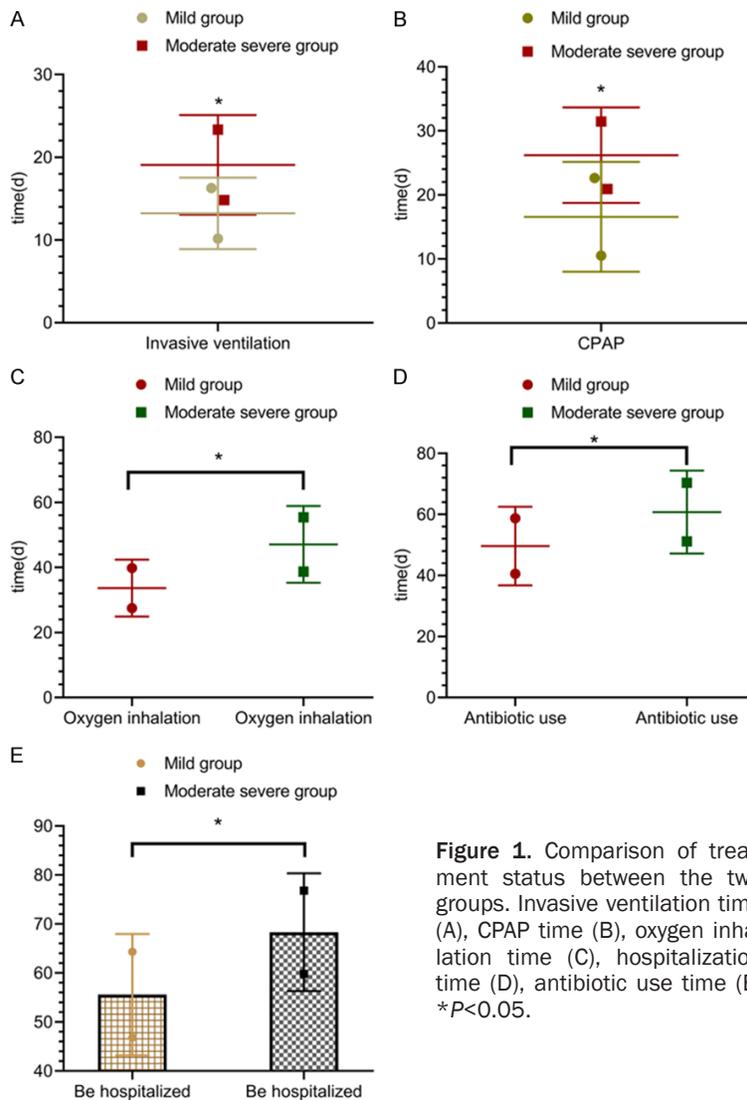
Figure 1. Comparison of treatment status between the two groups. Invasive ventilation time (A), CPAP time (B), oxygen inhalation time (C), hospitalization time (D), antibiotic use time (E) *$P<0.05$.

premature infants to reduce the risk of BPD. Although CPAP is non-invasive ventilation and its damage to premature infants is lighter than that of invasive ventilation, premature infants, especially those born very early, often have complicated medical problems, and CPAP will still affect the health status of them and increase the incidence of BPD [16, 17]. This study showed that combined pulmonary hypertension is an independent risk factor for the occurrence of BPD in preterm infants. A study on the risk factors of BPD in preterm infants has also shown that pulmonary hypertension is one of the risk factors [18]. According to the analysis, the reason may be that infants with moderate and severe BPD will likely exhibit signs and symptoms of respiratory distress syndrome, which decreases the blood flow to the non-ventilated lung, causing pulmonary hypertension. Pulmonary hypertension will impact the right ventricular load of the proportion of pulmonary and ventilation-blood flow will be unbalanced, and the blood flow will flow faster from right to left through the arterial catheter, leading to more severe hypoxia. Therefore, the ventilator cannot be withdrawn, prolonging duration of CPAP [19].

After 10 days of low-dose glucocorticoid treatment, the consumption rates of diuretics and fluconazole (3.77%, 62.26%) in the mild group were lower than those in the moderate-severe

study also showed that mild BPD accounted for the highest proportion of all children with BPD, which was more than 50% [8]. In this study, it was found that being small for gestational age, pulmonary hypertension, and CPAP duration were the independent risk factors for the occurrence of moderate to severe BPD, suggesting that pulmonary hypertension and long duration of CPAP should be monitored in
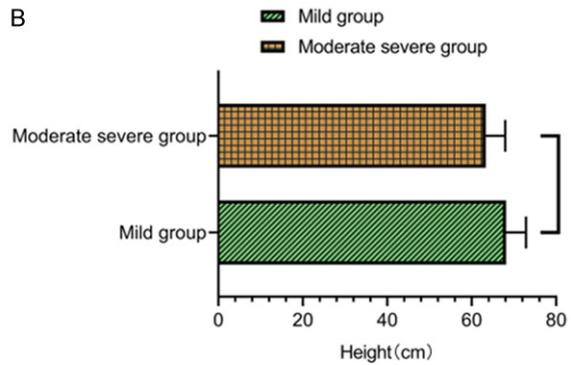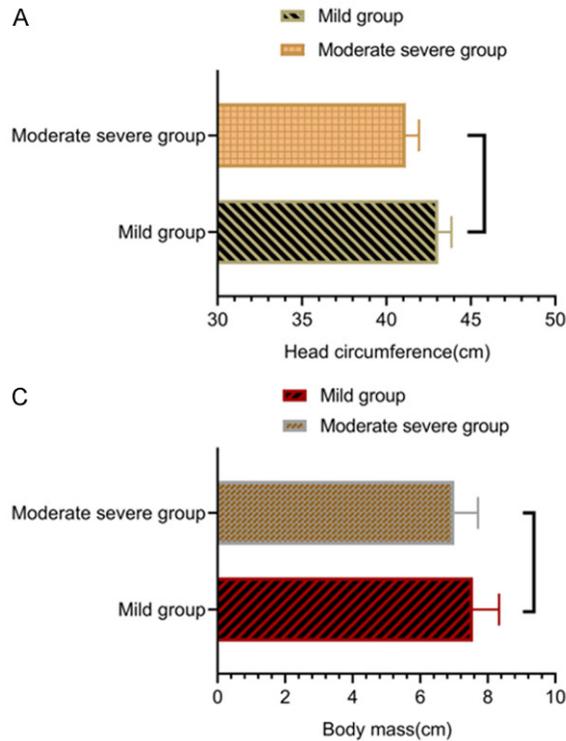
Figure 2. Comparison of head circumference, height, and body weight between the two groups. The head circumference (A), height (B), and body weight (C) at 6 months after birth in the mild group. *P<0.05.
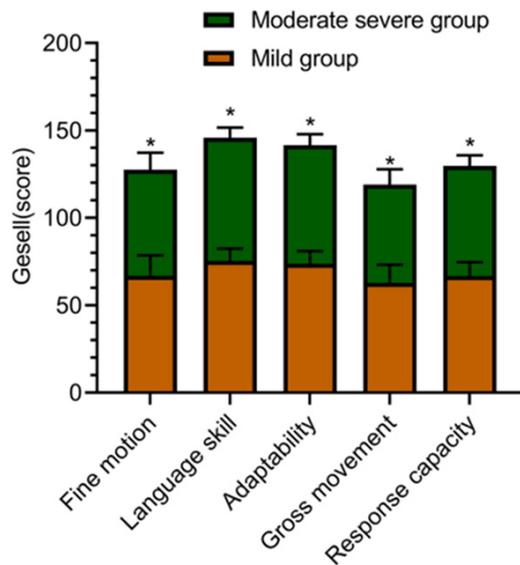

Figure 3. Comparison of Gesell scale scores between the two groups. Fine motor, language ability, ability to respond, gross motor, and physical ability, *P<0.05.

group (15.38%, 80.00%), and the duration of invasive ventilation, CPAP, oxygen inhalation, and hospitalization were all shorter, and antibiotics consumption was lower than those of the moderate-severe group (P<0.05), indicating

that if premature infants received earlier glucocorticoid treatment following BPD, their condition can be controlled more quickly and the consumption of drugs will be lower, which will in turn reduce the medical costs. In this study, the mild group had a larger head circumference, length and body weight than the moderate-severe groups at 6 months after birth (P<0.05). Some studies have suggested that the increase of body length of the preterm infants with BPD in the mild group was significantly greater than that of the moderate and severe groups within 6 months after glucocorticoid treatment, and the increase of the moderate group was greater than that of the severe group (P<0.05) [20]. This indicated that premature infants with BPD receiving earlier glucocorticoid treatment would have better physical development. The reason may be that the condition of BPD is controlled after receiving glucocorticoid therapy, and the physical development of preterm infants would not be affected by BPD. In this study, the mild group scored higher on Gesell scale than the moderate-severe group, suggesting that early glucocorticoid therapy can promote the development of nervous system in premature infants, improving premature infants' motor ability, coordination, and vision. However, there are
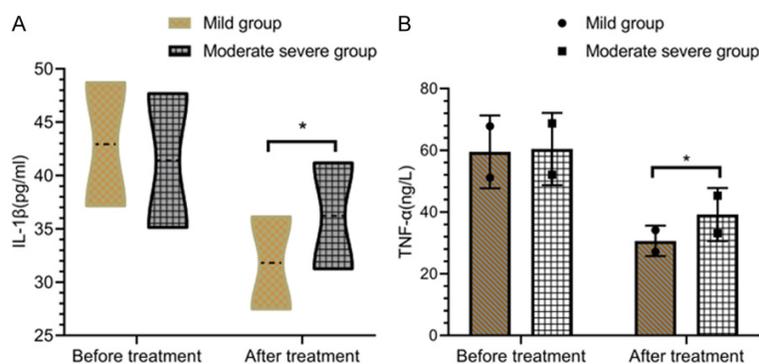
Figure 4. Comparison of the levels of inflammatory factors between the two groups. IL-1β (A) and TNF-α (B) *P<0.05.

Table 4. Comparison of survival rate and mortality during hospitalization between the two groups [n (%)]

Grouping	Number of cases	Survive	Death
Mild group	53	48 (90.57)	4 (9.43)
Moderate-severe group	65	51 (78.46)	14 (21.54)
X^2		4.255	
P		0.039	

also studies with different conclusions. A study has shown that preterm infants with BPD who have received glucocorticoid therapy do not have significant improvement in behavioral and cognitive abilities compared with those who have not received glucocorticoid therapy [21]. In this study, glucocorticoids were used to treat preterm infants diagnosed with BPD, and it was found that the development quotient of preterm infants was affected at 1-3 months, but they developed faster after 3 months than those without glucocorticoids treatment [22].

Studies have confirmed that the occurrence of BPD is related to the inflammatory response. Among them, TNF-α has a strong toxic effect on alveoli, it promotes the aggregation of inflammatory cells, and can accelerate the generation of other inflammatory cytokines. In addition, IL-1β is another inflammatory mediator that causes lung damage [23]. The levels of IL-1β and TNF-α in the mild group after treatment were lower than those in the moderate-severe group (P<0.05), indicating that a lower BPD level could lead to better efficacy of glucocorticoid treatment. Glucocorticoids can bind hormone receptors, have a direct effect on target cells, strengthen the stability of cell membranes, improve the osmotic pressure of

cells, and control the release of inflammatory products, and accelerate the secretion of pulmonary surfactant by alveoli, so as to control inflammatory levels [8]. In this study, the survival rate of the mild group was higher than that of the moderate-severe group (P<0.05), suggesting that early treatment could greatly improve the prognosis of preterm infants with mild BPD.

In summary, there are many risk factors for BPD in premature infants. Glucocorticoid therapy can promote physical development. The earlier use of glucocorticoids will have better effects. However, this study also has some shortcomings. The lack of comprehensive analysis of single factors for BPD could lead to risk factors being ignored. In addition, in the analysis of glucocorticoid therapy, there is no control group without glucocorticoid therapy, which may lead to some bias in the results.

Disclosure of conflict of interest

None.

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