Risk Factors That Affect the Degree of Bronchopulmonary Dysplasia in Very Preterm Infants: A 5-year Retrospective Study

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Abstract

Background

Bronchopulmonary dysplasia(BPD) is one of the most common adverse consequence of premature delivery and the most common chronic lung disease in infants. BPD is related to long-term lung diseases and neurological development disorders, particularly respiratory and nervous system damage can be sustained to adulthood. The adverse effects caused by severe BPD are more prominent, but there were few studies on the risk factors of different degrees of BPD.

Methods

This is a retrospective study of preterm infants born before 32 gestational weeks(GA) with bronchopulmonary dysplasia.

Results

250 preterm infants with BPD GA< 32 weeks were enrolle(137 boys[54.8 %] and 113 girls[45.2 %]). The birth weight ranged from 700g to 2010g (average birth weight 1318.52g). The GA was 25~31^{+6} weeks (average GA 30.0 weeks). There were 39 (15.6 %), 185 (74.0 %) and 26 (10.4 %) cases of mild, severe and severe BPD respectively. There were significant differences in birth weight and in the rate of intrauterine asphyxia, pulmonary hemorrhage, neonatal respiratory distress syndrome (NRDS), circulatory failure, pulmonary hypertension, patent ductus arteriosus(PDA), pulmonary surfactant(PS), aminophylline, caffeine, glucocorticoids, tracheal intubation, diuretics, and parenteral nutrition length among the three groups(*P*<0.05). Birth weight(aOR=0.993,95%*CI*:0.989~0.997) and duration of parenteral nutrition(aOR=2.966,95%*CI*:1.992~4.415) are independent risk factors for the moderate BPD, and birth weight(aOR=0.997, 95%*CI*:0.995~0.999) , duration of parenteral nutrition(aOR=1.163, 95%*CI*:1.017~1.329), PDA (aOR=4.325, 95%*CI*:1.457~12.997) and aminophylline (aOR=4.882, 95%*CI*:1.661~14.350) are independent risk factors for the severe BPD, while caffeine (aOR=0.167, 95%*CI*: 0.052~0.538)was a protective factor for severe BPD.

Conclusion

Low birth weight and longer duration of parenteral nutrition were independent risk factors for moderate or severe BPD. PDA and aminophylline were independent risk factors of severe BPD, while caffeine was a protective factor for severe BPD.

Trial registration

retrospectively registered.

Background

BPD is a chronic lung disease. Northway[1] reported BPD for the first time in 1967. However, the definition and characteristics of BPD have changed over the past decades years [1, 2]. The new definition of BPD is more comprehensive, with oxygen support at least 28 days as required, and further classifies severity as mild, moderate or severe according to oxygen demand after 36 weeks of corrected GA[2] .

In recent decades, due to the progress of perinatology and neonatal care, such as prenatal corticosteroids and exogenous surfactant treatment, the survival rate of premature infants has been significantly improved. Many complications related to premature delivery, such as respiratory distress syndrome (RDS), ventricular hemorrhage and necrotizing enterocolitis (NEC), have shown a significant decrease. However, BPD remains one of the most common complications in preterm infants [3, 4]. Moreover, the prevalence rate of BPD is increasing, probably due to the increase in the survival rate of very premature infants [5]. According to studies of different neonatal networks in many countries, including the United States, Canada, South Korea, China and India, the prevalence of BPD reportedly varies greatly, ranging from 11 to 50 per cent, due to different diagnostic and management criteria [6]. The incidence of BPD increases with the decrease of GA and birth weight. About 30% of extremely premature infants suffer from BPD [7], 40 – 50% of extremely low premature infants suffer from BPD [4, 8], and the incidence of infants with gestational age less than 25 weeks is as high as 80%[9].

Newborns affected by BPD have higher mortality[10] and increased rates of pulmonary, cardiovascular, and neurodevelopmental disorders in surviving newborns, leading to reduced quality of life and increased resource consumption [11, 12]. Premature infants with severe BPD are particularly difficult to manage and are more prone to a variety of complications and comorbidities, including prolonged hospitalization, family respiratory support and death [13, 14]. The mortality rate of premature infants with severe BPD is as high as 25%, and the readmission rate of surviving premature infants in the first year is as high as 50%. The developmental disorder of nervous system is 2-3 times higher than that of normal infants, which has become one of the important factors affecting the quality of life of surviving premature infants. Therefore, it’s particularly important to avoid severe BPD.

In the past decades, many clinical prediction models have been developed and published. Previous studies have found that the incidence of BPD increases with the decrease of gestational age and birth weight. Other perinatal factors affecting it include male gender [15], intrauterine growth restriction[16], chorioamnionitis[17], smoking [18], and race / nation[16]. Postnatal factors also increase the risk of BPD and adverse outcomes, including RDS at birth, the need for invasive mechanical ventilation, pulmonary inflammation, pulmonary vascular disease, infection, PDA and undernutrition[19]. However, most studies at home and abroad focus on the pathogenesis and clinical risk factors of BPD, and there are few studies on the risk factors affecting the occurrence of different degrees BPD. It is not clear whether the above factors will lead to the moderate or severe BPD. Therefore, early detection of risk factors for different degrees of BPD to guide clinical implementation of targeted interventions is conducive to avoiding and minimizing the occurrence of moderate and severe BPD, reducing the risk of respiratory and neurodevelopmental disorders, improving the quality of life in childhood or adulthood and reducing social and family burden.

This study comprehensively analyzed the sociodemographic data of premature infants with different degrees of BPD, clinical related treatment and clinical complications, in order to find out the risk factors affecting the severity of BPD.

Methods

Study design and participants

This is a retrospective study. All premature infants diagnosed as BPD in the First People ' s Hospital of Yunnan Province from January 1, 2016 to December 31, 2020 were included. All patients were screened strictly according to BPD diagnostic criteria [3]. Preterm infants with GA ≥32 weeks or born outside the hospital, as well as preterm infants with severe malformations, chromosomal abnormalities, genetic metabolic diseases or incomplete information were excluded. 250 premature infants with BPD whose GA≤32 weeks were selected as the research objects. Informed consent was waived by the Ethics Committee of the First People's Hospital of Yunnan Province due to the retrospective nature of this study.

Study factors

We selected the possible risk factors according to the variables reported in previous studies about the risk factors of BPD or about the related pathophysiological mechanisms of BPD to explore the risk factors of different degrees of BPD. All methods are in accordance with relevant guidelines and provisions.We collected the following data:

(1)Sociodemographic variable and perinatal factors: gender, GA, birth weight, intrauterine asphyxia, amniotic fluid pollution, placental abrusption, premature rupture of membranes, maternal age greater than or equal to 35 years old, prenatal use of glucocorticoids to promote fetal lung maturation, gestational diabetes, gestational hypertension, hyperthyroidism, hypothyroidism, maternal anemia, prenatal fever.

(2)Clinical complications: septicemia, sepsis, pneumonia, infection, NEC, apnea, respiratory failure, pulmonary hemorrhage, acute respiratory distress syndrome(ARDS), neonatal respiratory distress syndrome(NRDS), circulatory failure, anemia, pulmonary hypertension, PDA, hypoproteinemia, electrolyte disorder, retinopathy of prematurity(ROP), intraventricular hemorrhage, intracranial hemorrhage, and paraventricular leukomalacia.

(3)Treatment measures: pulmonary surfactant(PS), aminophylline, caffeine, glucocorticoid hormones, diuretics, noninvasive assisted breathing, tracheal intubation, intravenous nutrition, oxygen concentration greater than or equal to 40%.

Ethics

This study was approved by the Ethics committee of The First People's Hospital of Yunnan Province(Ethic number:KHLL2021-KY001).

Statistical analysis

SPSS 26.0 was used for statistical analysis. Chi-square test or Fisher exact test was used to compare categorical variables. For continuous data, if they conform to normal distribution and have uniform variance, they are described as mean and standard deviation, and one-way analysis of variance is adopted. If it does not conform to the normal distribution, it is described as the median, 25th percentile and 75th percentile, using Kruskal-Wallis test. In the single factor analysis, stepwise screening method was used to screen statistically significant variables. The final selected factors are used as hybrid factors to calculate the adjusted advantage ratio, the maximum likelihood ratio and the corresponding 95% confidence interval. All hypothesis tests were double-tailed, P < 0.05was statistically significant.

Results

In this study, we collected 388 preterm infants with BPD, excluding 105 preterm infants with GA ≥32 weeks or born outside the hospital, as well as 6 cases of severe malformations, 2 cases of chromosomal abnormalities, 4 cases of genetic metabolic diseases, 21 cases of incomplete information. Finally, 250 premature infants with BPD whose GA 32 weeks were selected as the research objects(Fig. 1). Among the 250 preterm infants with BPD, 137 (54.8%) were male and 113 (45.2%) were female. The birth weight ranged from 700g to 2010 g, with an average birth weight of 1318.52 ± 255.45 g. The GA was $25\sim31^{+6}$ weeks, with an average GA of 30.0 (28.8, 31.0) weeks. Among these infants with BPD included in this study,there were 23 cases (9.2%) preterm infants whose GA < 28 weeks.

The antenatal features and demographic of premature infants with different degrees of BPD are summarized(Table 1). The significant differences in birth weight and the rate of intrauterine asphyxia among the three groups can be seen(P<0.05). There were no significant differences among the three groups in the rates of male, GA, placental abruption, premature rupture of membranes, amniotic fluid pollution, maternal age greater than or equal to 35 years, gestational hypertension, gestational diabetes, hypothyroidism, hyperthyroidism, anemia, prenatal fever, prenatal use of glucocorticoids to promote fetal lung maturity.

Table 1. Demographic features of preterm infants with different levels of BPD

Variables	Mild BPD （n=39）	Moderate BPD （n=185）	Severe BPD （n=26）	c^2/H/F	*P*
Male(n,%)	23(58.9)	98(52.9)	16(61.5)	1.000	0.606#
Gestational age [weeks,M(P25,P75)][a]	30.1(29.7,31.0)	30.0(28.8,30.8)	29.9(28.4,31.0)	2.291†	0.318
Birth weight (g,mean±S)[b]	1,471.5±213.5	1,308.7±246.3	1,158.8±265.5	13.431‡	<0.001
Asphyxia (n,%)	13(33.3)	87(47.0)	19(73.0)	9.973	0.007#
Placental abruption (n,%)	0(0)	4(2.1)	0(0)	0.043	0.837*
Premature rupture of membranes (n,%)	17(43.5)	82(44.3)	13(50)	0.324	0.850#
Amniotic fluid contamination (n,%)	0(0)	1(0.5)	1(3.8)	2.378	0.123*
Age≥35 years(n,%)	9(23.0)	45(24.3)	10(38.4)	2.547	0.280#
Gestational hypertension (n,%)	6(15.3)	40(21.6)	7(26.9)	0.011	0.918*
Diabetes (n,%)	9(23.0)	50(27.0)	5(19.2)	0.882	0.643#
Hyperthyroidism(n,%)	0(0)	4(2.1)	0(0)	0.043	0.837*
Hypothyroidism (n,%)	2(5.1)	12(6.4)	5(19.2)	4.356	0.113*
Anemia (n,%)	3(7.6)	6(3.2)	1(3.8)	1.396	0.498*
Antenatal fever(n,%)	1(2.5)	6(3.2)	0(0)	0.230	0.631*
Use of hormones to promote lung maturation(n,%)	3(7.6)	11(5.9)	2(7.6)	0.236	0.889*

[a] Kruskal-Wallis test, [b] one-way ANOVA, the rest using chi-square test; †H value, ‡F value, the rest are c^2 values; * Fisher's exact probability method, # Pearson's chi-square value.

The clinical complications of premature infants with different degrees of BPD were summarized(Table 2). It can be seen that the differences in the rate of pulmonary hemorrhage, NRDS, circulatory failure, pulmonary hypertension and PDA were statistically significant among the three groups(*P*<0.05). There were no significant differences in septicemia, sepsis, pneumonia, infection, NEC, apnea, respiratory failure, ARDS, anemia, hypoproteinemia, electrolyte disturbance, retinopathy of prematurity, intraventricular hemorrhage, intracranial hemorrhage, or paraventricular leukomalacia among the three groups .

Table 2
Complications of preterm infants with different levels of BPD

Variables	Mild BPD(n=39)	Moderate BPD (n=185)	Severe BPD (n=26)	χ^2	*P*
Septicemia(n,%)	0(0)	3(1.6)	1(3.8)	1.435	0.231
Sepsis(n,%)	2(5.1)	28(15.1)	6(23.0)	4.944	0.084*
NEC(n,%)	1(2.5)	6(3.2)	1(3.8)	0.087	0.769*
Infection(n,%)	18(46.1)	115(62.1)	14(53.8)	3.701	0.157
Pneumonia (n,%)	21(53.8)	98(52.9)	10(38.4)	2.016	0.365
Apnea(n,%)	4(10.2)	38(20.5)	7(26.9)	3.149	0.207
Respiratory failure(n,%)	0(0)	7(3.7)	2(7.6)	2.718	0.099
Pulmonary hemorrhage(n,%)	1(2.5)	19(10.2)	10(38.4)	17.052	<0.001*
NRDS(n,%)	7(17.9)	81(43.7)	19(73.0)	19.647	<0.001
ARDS(n,%)	0(0)	2(1.0)	0(0)	0.021	0.884*
Circulatory Failure(n,%)	0(0)	28(15.1)	6(23.0)	13460	0.001*
Pulmonary hypertension(n,%)	0(0)	0(0)	1(3.8)	4.301	0.038*
Anemia (n,%)	35(89.7)	165(89.1)	26(100.0)	5.569	0.062*
Patent ductus arteriosus (n,%)	5(12.8)	53(28.6)	12(46.1)	8.746	0.013
Hypoproteinemia(n,%)	21(53.8)	116(62.7)	20(76.9)	3.566	0.168
Electrolyte disorders(n,%)	17(43.5)	86(46.4)	17(65.3)	3.622	0.164
ROP(n,%)	6(15.3)	40(21.6)	4(15.3)	1.169	0.557
Paraventricular white matter softening(n,%)	1(2.5)	3(1.6)	0(0)	0.617	0.432*
Intraventricular hemorrhage(n,%)	0(0)	1(0.5)	0(0)	0.011	0.918*
Intracranial hemorrhage(n,%)	7(17.9)	44(23.7)	7(26.9)	0.841	0.657

*Fisher's exact probability method, the rest are Pearson's chi-square values. *ARDS*:Acute Respiratory Distress Syndrome, *NEC*: Necrotizing Enterocolitis, *NRDS*: Neonatal Respiratory Distress Syndrome, *ROP*: Retinopathy Of Prematurity.

Treatment measures of premature infants with different degrees of BPD were compared(Table 3). The following conclusions were drawn : the rates of PS, aminophylline, caffeine, glucocorticoids, tracheal intubation, diuretics, or parenteral nutrition were statistically significant among the three groups(P<0.05);

there were no significant differences in the maximum oxygen concentration ≥ 40% or noninvasive assisted respiration.

Table 3
Treatment in preterm infants with different levels of BPD

Variables	Mild BPD (n=39)	Moderate BPD (n=185)	Severe BPD (n=26)	χ^2/H	*P*
PS(n,%)	6(15.3)	85(45.9)	19(73.0)	22.166	<0.001#
Aminophylline(n,%)	4(10.2)	20(10.8)	11(42.3)	14.522	0.001*
Caffeine(n,%)	15(0.38)	128(69.1)	11(42.3)	17.423	<0.001#
Glucocorticoids(n,%)	37(94.8)	140(75.6)	26(100.0)	20.606	<0.001*
Non-invasive respiratory support(n,%)	37(94.8)	180(97.2)	26(100.0)	1.532	0.217*
Invasive respiratory support(n,%)	10(25.6)	111(60.0)	21(80.7)	22.291	<0.001#
Maximum concentration of oxygen used≥40%(n,%)	24(61.5)	131(70.8)	22(84.6)	4.019	0.134#
Parenteral nutrition(days,M(P25,P75))[a]	10(8,12)	17(15,20)	19(16,22)	82.257†	<0.001
Diuretics(n,%)	19(48.7)	50(27.0)	15(57.6)	14.342	0.001#

[a] Kruskal-Wallis test, the rest using chi-square test; †H value, the rest are χ^2 values; * Fisher's exact probability method, # Pearson's chi-square value.*PS* Pulmonary Surfactant.

In univariate analysis, 14 variables were statistically significant. Multivariate logistic regression analysis was used because the data among the three groups did not meet the parallel test. The results show that lower birth weight and longer duration of parenteral nutrition are independent risk factors for the moderate BPD, and lower birth weight, longer duration of parenteral nutrition, PDA and aminophylline are independent risk factors for the severe BPD, while caffeine is a protective factor for severe BPD(Table 4).

Table 4
Correlative factors for moderate or severe BPD in preterm infant

	β	SE	Wald	aOR	95%*CI*	*P*
Preterm infants with moderate BPD compared with preterm infants with mild BPD						
Birth weight (g)	-0.007	0.002	10.803	0.993	0.989~0.997	0.001
Parenteral nutrition(days)	1.087	0.203	28.686	2.966	1.992~4.415	<0.001
Preterm infants with moderate BPD compared with preterm infants with severe BPD						
Birth weight (g)	0.003	0.001	8.405	1.003	1.001~1.005	0.004
Parenteral nutrition(days)	-0.151	0.068	4.885	0.860	0.752~0.983	0.027
Patent ductus arteriosus	-1.471	0.558	6.938	0.230	0.077~0.686	0.008
Caffeine	1.791	0.597	8.988	5.997	1.859~19.343	0.003
Aminophylline	-1.586	0.550	8.308	0.205	0.070~0.602	0.004
Preterm infants with severe BPD compared with preterm infants with mild BPD						
Birth weight (g)	-0.009	0.002	17.007	0.991	0.986~0.995	<0.001
Parenteral nutrition(days)	1.201	0.211	32.333	3.324	2.197~5.029	<0.001
Patent ductus arteriosus	2.580	1.204	4.591	13.193	1.246~139.676	0.032
Preterm infants with severe BPD compared with preterm infants with moderate BPD						
Birth weight (g)	-0.003	0.001	8.405	0.997	0.995~0.999	0.004
Parenteral nutrition(days)	0.151	0.068	4.885	1.163	1.017~1.329	0.027
Patent ductus arteriosus	1.471	0.558	6.938	4.325	1.457~12.997	0.008
Caffeine	-1.791	0.597	8.988	0.167	0.052~0.538	0.003
Aminophylline	1.586	0.550	8.308	4.882	1.661~14.350	0.004

aOR adjusted odds ratio, *95% CI* 95% confidence interval.

Discussion

Previous research reports mostly focused on premature infants with BPD and non-BPD. A variety of risk factors that may make infants susceptible to BPD have been identified in clinical and experimental studies[20]. BPD is one of the main diseases that lead to long-term hospitalization, high cost of hospitalization and poor long-term prognosis of premature infants. In particular, the abnormality of respiratory and nervous system in premature infants with moderate or severe BPD has become the most concerned problem for neonatal intensive care unit(NICU) medical staff. Therefore, exploring the risk

factors of moderate or severe BPD is crucial to alleviate the severity of BPD, improve the prognosis of children and improve their short-term and long-term quality of life.

The data of this study suggests that lower birth weight increases the incidence of moderate / severe BPD. In our study, there was no significant difference in GA among the three groups preterm infants with different degrees of BPD, but the difference in birth weight was statistically significant, suggesting that there may be more premature infants with growth restriction in these infants with moderate or severe BPD. Studies had shown that fetal growth restriction(FGI) increases the risk of BPD in premature infants[16, 21], and the severity of FGI can affect alveolarization and angiogenesis. More and more literatures support that FGI is an important factor in early lung structure and function damage[22]. Chronic hypoxia and malnutrition affect the development of lung parenchyma, airway and vascular system, resulting in high incidence of BPD [22, 23]. In premature infants with FGI, pulmonary vessels thickened and elasticity decreased[21]. The role of arterial stiffness seems to be crucial for BPD. On the one hand the arteries lack of buffer, making the heart afterload increased ; on the other hand, pulmonary vascular is exposed to higher resistance stress, thereby accelerating microvascular disease[24]. Abnormal angiogenesis seems to be a feature of the pathogenesis of BPD. This angiogenesis damage can be evaluated by measuring pulmonary vascular resistance and the thickness of the main pulmonary artery by ultrasound.

Our research data shows that the duration of parenteral nutrition is an independent risk factor for moderate or severe BPD. Premature infants usually cannot tolerate enteral feeding well [25], they rely on parenteral nutrition to meet the energy demand ,to provide necessary nutrition, and to optimize the growth and development in the first week after birth. PN is a common clinical practice, which provides some short-term development benefits for premature infants. However, PN increases the oxidant load of premature infants, and its components may cause oxidative stress and inflammation. Inflammation and oxidative stress are the main causes of BPD in premature infants. Premature infants have low tolerance to fat emulsion that is an important part of PN. The use of fat emulsion can lead to serious complications, such as impaired lung gas exchange, increased pulmonary vascular resistance, enhanced oxidative stress, cholestatic liver disease and adverse immune response. These complications are related to BPD in premature infants[26].

The incidence of PDA is high in very low birth weight premature infants. PDA is another important risk factor for BPD was confirmed [27]. However, there is little data on whether PDA is associated with the severity of BPD. The incidence of PDA is higher in premature infants with severe BPD than with moderate BPD, while it is not different between premature infants with mild BPD and with moderate BPD, suggesting that PDA may be a factor that promotes severe BPD happening. Studies on the mechanism of PDA increasing the incidence of BPD have shown that excessive shunt of blood through PDA from left to right will lead to fluid congestion in pulmonary interstitial, infiltration of protein liquid into alveolar space, and disruption of the function of surfactant, which eventually leads to deterioration of lung mechanics[28]. In addition, Evidences show that there is a dose-dependent relationship between catheter blood flow [29], contact length with PDA [30] and BPD risk. The decline of lung compliance caused by

PDA requires larger pulmonary dilatation pressure and more oxygen demand, which to some extent leads to lung injury in premature infants. However, there is no definite result in random clinical trials to support or refute this hypothesis.

Our results suggest that caffeine may be a factor to avoid the development of severe BPD. Caffeine treatment of premature infants with apnea test confirmed that caffeine significantly reduced the occurrence frequency of BPD[31, 32], and data [31, 33] supported that caffeine could reduce the severity of BPD, but there was no randomized controlled experiment to confirm this. Data show that caffeine can reduce the risk of BPD through several mechanisms [34, 35], the most important of which is lung protection. Caffeine increases the sensitivity of central nervous system to blood carbon dioxide levels by increasing nerve excitability [34, 35], and increases diaphragm drift, respiratory tidal volume and minute ventilation [34, 35, 36], thereby reducing the demand for respiratory support and oxygen supplement[37]. Caffeine also reduces respiratory support by improving respiratory resistance, improving lung compliance and functional residue, and increasing respiratory muscle strength [34, 35, 38]. In addition, studies have shown that caffeine has protective antioxidant and anti-inflammatory effects, improving alveolarization and pulmonary angiogenesis [34, 35, 38, 39],but this theory has not been fully accepted [35, 40].

In summary, our results suggest that low birth weight, parenteral nutrition length, PDA and aminophylline may be independent risk factors for severe BPD,and caffeine is a protective factor to avoid severe BPD. However, our research has certain limitations. First, this is a retrospective study, our data may be biased ; secondly, this is a single-center study for preterm infants born in China (GA < 32 weeks). Our results should be carefully extended to other environments. Finally, the definitions of some factors used in our investigation may be inconsistent with those used in other studies. However, in this study, we strictly use BPD diagnostic criteria and risk factors to study the risk factors of BPD severity. Our conclusions should have certain guiding significance for future multicenter prospective trials.

Conclusions

Birth weight, length of parenteral nutrition, PDA and aminophylline may be independent risk factors of moderate or severe BPD. Caffeine is a protective factor to avoid severe BPD. Avoiding low birth weight premature infants, shortening duration of parenteral nutrition, early treatment of PDA, reducing aminophylline use and rational use of caffeine may prevent severe or moderate BPD.

List Of Abbreviations

ARDS
Acute respiratory distress syndrome
BPD
Bronchopulmonary dysplasia
FGI
Fetal growth restriction

GA
Gestational age
NEC
Necrotizing enterocolitis
NICU
Neonatal intensive care unit
NRDS
Neonatal respiratory distress syndrome
PDA
Patent ductus arteriosus
PS
Pulmonary surfactant
RDS
Respiratory distress syndrome
ROP
Retinopathy of prematurity

Declarations

Ethics approval and consent to participate

Informed consent was waived by the Ethics Committee of the First People's Hospital of Yunnan Province due to the retrospective nature of this study. This study was approved by the Ethics committee of The First People's Hospital of Yunnan Province(Ethic number:KHLL2021-KY001).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

none.

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Authors' contributions

J.H Yang and C.H. Tang conceptualized and designed this study. T.F. Dong, L. Liang, F. Xu, Y.F. He, C.L. Li， F. Luo and J.H. Liang was responsible for collecting data. T.T. Yang，Q.Q. Shen and S.Y. Wang were responsible for analyzing and interpretation of data. T.T. Yang and Q.Q. Shen drafted the initial manuscript, and T.T. Yang, S.Y. Wang, J.H Yang and C.H. Tang reviewed and revised the manuscript. J.H Yang and C.H. Tang approved the final manuscript submitted, and agreed to be responsible for all aspects of the work.

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Figures

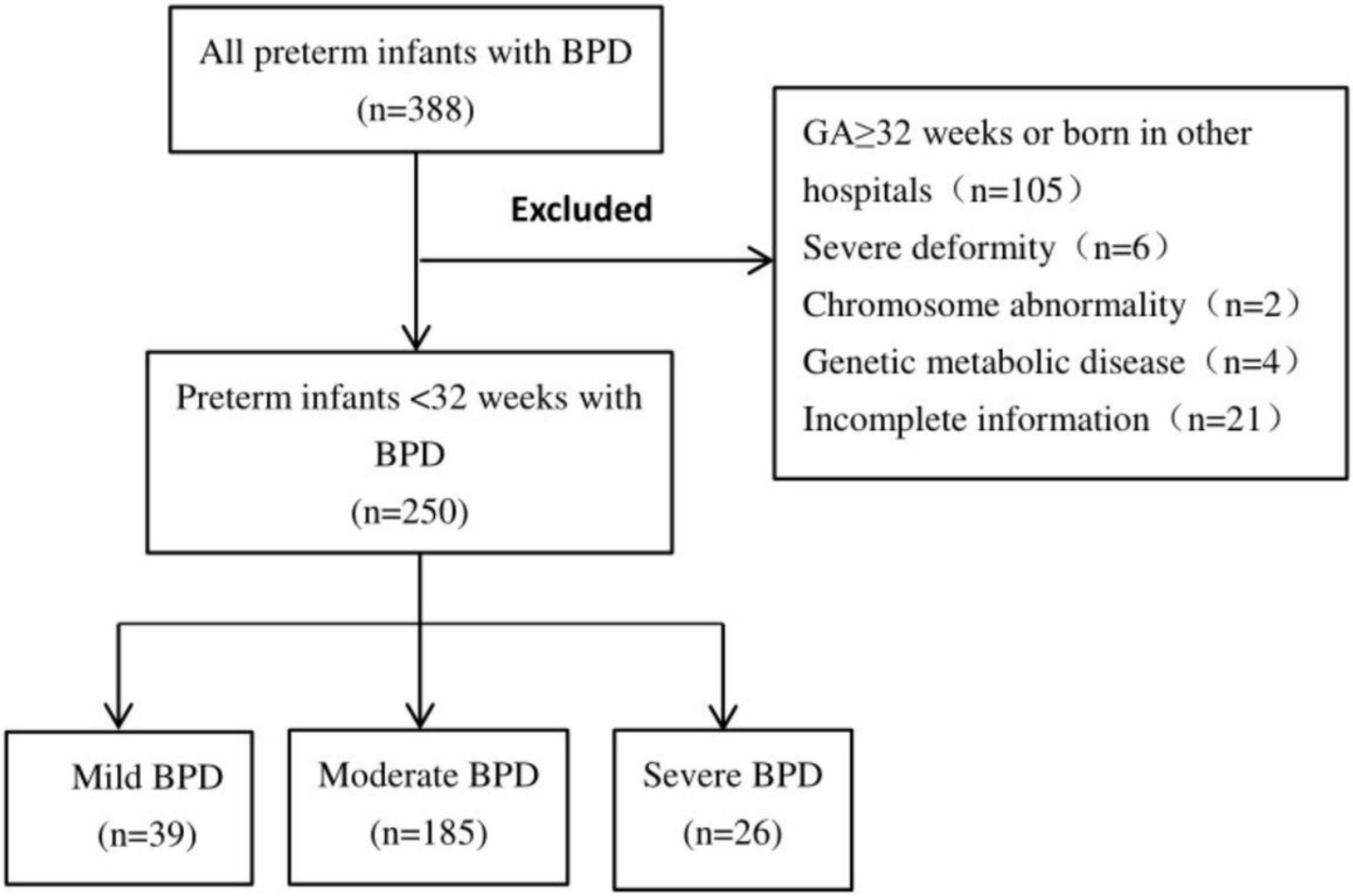

Figure 1

Flow chart in selection of preterm infants with BPD.