A multicenter prospective cohort trial protocol – Risk factors for Bronchopulmonary Dysplasia in Chinese preterm infants

Background

The development of perinatal medicine improved the survival rate of premature infants especially extremely low birth weight (VLBWI). But the incidence of severe lung disease, bronchopulmonary dysplasia(BPD), was not significantly reduced or even increased. BPD is the primary complication in the neonatal intensive care unit (NICU), which not only has adverse effect on the lung function, also affects slow growth and neurodevelopment. As the disease of extended hospitalization and medical cost, BPD has become an important issue in the NICU.

At present the application of antenatal corticosteroids and the improvement of treatment technology, the diagnosis standard of BPD is constantly evolving. The definition of BPD had changed from 1969 (Northway) to 2001(NICHD). In 2018, NICHD update the BPD international workshop classification standard.

However, the risk factors and intervention of BPD remains further study. It is particularly important to explore more effective preventive and control measures, which is of great practical significance to promote the development of perinatal and neonatal medicine. The aim of our work is to examine the risk factors for BPD in the Chinese population of preterm infants born at < 32 week gestation with respiratory distress.

Methods/Design

Study design

Our study will be a multicenter prospective cohort trial, which utilize a large dataset collected from 39 tertiary referral NICUs in China. A total of more than 1000 preterm infants born at < 32 week gestation with respiratory distress will be recruited. All items from the World Health Organization Trial Registration Data Set are shown in Table1.

Table 1 Items from the World Health Organization Trial Registration Data Set

Data Category	Information
Registration number	ChiCTR2000030125 Chinese clinical trial registry
Scientific title	Risk factors for Bronchopulmonary Dysplasia in preterm infants: a multicenter prospective cohort study in China
Approval of ethic committee	Medical Ethics Committee of the Children's Hospital Zhejiang University School of Medicine
Ethical approval project identification code	2019-IRB-164
Date of approved by ethic committee	2019/12/24
Study type	Prospective observational study
Study design	Factorial
Inclusion criteria	Preterm infants admitted within 72 hours after birth, gestational age <32 weeks and respiratory distress score >= 5
Exclusion criteria	Congenital structural malformations such as complex congenital heart disease,

	diaphragmatic hernia, anomalies of digestive tract/kidney, and genetic metabolic disorders
Drop-out criteria	Death within 14 days after birth or give up treatment within 36 weeks PMA
Study execute time	From01/01/2020To 31/12/2021
Primary Outcomes	Early death (between 14 days of postnatal age and 36 weeks PMA) and BPD (36 weeks PMA)
Secondary outcomes	The grade and severity of BPD
Recruitment start date	01/03/2020
Recruitment end date	28/02/2021

Participants

Patients will be recruited from 39 tertiary referral NICUs in China. The inclusion criteria are as follows: Preterm infants admitted within 72 hours after birth, gestational age <32 weeks and respiratory distress score >= 5. The exclusion criteria are as follows: Congenital structural malformations such as complex congenital heart disease, diaphragmatic hernia, anomalies of digestive tract/kidney, and genetic metabolic disorders. The drop-out criteria are as follows: Death within 14 days after birth or give up treatment within 36 weeks PMA.

The following hospitals have committed to participate in the study: The Children's Hospital, Zhejiang University School of Medicine, Children's Hospital of Chongqing Medical University, Women's Hospital School Of Medicine Zhejiang University, Shanghai Children's Hospital Shanghai Jiaotong University School of Medicine, The Affiliated Obstetrics and Gynecology Hospital of Nanjing Medical University, Ningbo Women and Children's Hospital, Shenzhen Maternity & Child Healthcare Hospital, The First Hospital of Jilin University, Bethune International Peace Hospital of PLA, The Fifth Medical Center of Chinese PLA General of Hospital, The First Hospital of Tsinghua University, Peking University Third Hospital, Quanzhou Women's and Children's Hospital, Chongqing Health Center for Women and Children, Chengdu Women's & Children's Central Hospital, Guizhou Maternity and Child Health Care Hospital, The First Affiliated Hospital of Guangxi Medical University, The Second Affiliated Hospital of Guangxi Medical University, The Maternal & Child Health Hospital of Guangxi Zhuang Autonomous Region, The First Affiliated Hospital of Kunming Medical University, The Second Affiliated Hospital of Kunming Medical University, Kunming Children's Hospital, The First Affiliated Hospital of Zhengzhou University, Henan Children's Hospital, Henan Provincial People's Hospital, Shaanxi Provincial People's Hospital, The First Affiliated Hospital of Xinjiang Medical University, The People's Hospital of Xinjiang Uygur Autonomous Region, Qinghai Provincial Women & Children's hospital, Inner Mongolia People's Hospital, Gansu Provincial Maternity and Child-Care Hospital, Xuzhou Children's Hospital, Yulin Maternity & Child Healthcare Hospital, Chinese Traditional Medicine Affiliated Hospital of Southwest Medical University, Qujing Maternity & Child Healthcare Hospital, Taian Maternal and Child Health Hospital, The Second Affiliated Hospital of Ningxia Medical University, Mianyang Central Hospital, Chongqing Three Gorges Central Hospital.

Ethics

The study protocol has been reviewed and approved by the Medical Ethics Committee of the

Children's Hospital Zhejiang University School of Medicine. Ethical approval project identification code is 2019-IRB-164. The study will be carried out according to the principles of the Declaration of Helsinki.

Enrollment

Clinicians will approach eligible parents for consent. The clinicians will explain the study verbally and deliver printed information sheets describing the purpose and process of the study (Fig.1). All parents will read the informed consent form, voluntarily agree to participate in this study and sign the informed consent form prior to the study. Written informed consent will be obtained from each participants before enrolment in the study, and then preserved by researchers. Infants whose parents decline to consent will receive standard care.

Fig.1 Study Schedule enrollment, intervention, and assessment.

Items	**Admition**	**13 days after birth**	**14 days after birth ~ 36 weeks PMA**	**36 weeks PMA**
Informed consent	**X**			
Inclusion criteria	**X**			
Exclusion criteria	**X**			
Drop-out criteria		**X**	**X**	
Factors during pregnancy	**X**			
Labor factors	**X**			
Postnatal factors			**X**	
Assessment Outcomes				**X**

Study procedure

This multicenter prospective cohort study aims to investigate factors during pregnancy (situation, illness, drug), labor (delivery mode, premature rupture of membranes, amniotic fluid, birth asphyxia, etc.) and postnatal (respiratory support, infection status, nutrition liquid, circulation management, drug applications) , and to explore the risk factors for BPD (Fig.2).

The Primary outcomes are early death (between 14 days of postnatal age and 36 weeks PMA) and BPD (36 weeks PMA). The secondary outcomes are the grade and severity of BPD. (36 weeks PMA). The outcomes of the study are measured definition of BPD according to the definition of 2018 NICHD BPD-workshop (Table 2) .

Table 2 The definition of 2018 NICHD BPD-workshop

A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires 1 of the following FiO_2 ranges/oxygen levels/O_2 concentrations for 3 consecutive days to maintain arterial oxygen saturation in the 90%–95% range.

Grades	Invasive IPPV*	N-CPAP, NIPPV, or nasal cannula 3 L/min	Nasal cannula flow of 1–<3 L/min	Hood O_2	Nasal cannula flow of <1 L/min
I	—	21	22–29	22–29	22–70
II	21	22–29	30	30	>70
III	>21	30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

* Excluding infants ventilated for primary airway disease or central respiratory control conditions. Values are percents.

CPAP, continuous positive airway pressure; *IPPV*, intermittent positive pressure ventilation; *N-CPAP*, nasal continuous positive airway pressure; *NIPPV*, noninvasive positive pressure ventilation.

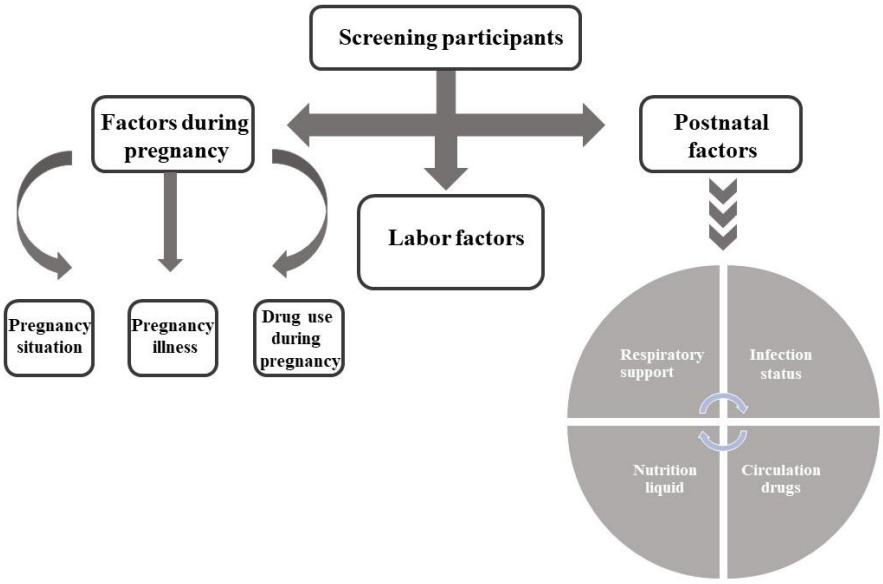

Fig.2 Procedure of the study

Statistical analysis

We will use univariate logistic regression analysis to assess the risk factors for the development of BPD. Odds ratios (ORs) with corresponding 95% confidence intervals are computed for the analyzed clinical and exposure variables. Subsequently, a multiple logistic regression model iss developed using stepwise backward elimination to evaluate risk factors for the development of BPD and to calculate odds ratios (ORs). Selected continuous variables (duration of mechanical ventilation, timing of caffeine and surfactant) are dichotomized for the logistic regression analysis.

To describe the demographic and clinical parameters, we present the categorical variables as absolute and relative frequencies and the continuous variables as the means (standard deviations). The Kruskal–Wallis test is used to check for the differences in frequencies. All percentages were calculated according to the number of patients for whom data were available. p values less than 0.05 were considered significant.