



The application value of lung ultrasound findings in preterm infants with bronchopulmonary dysplasia

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Background: The purpose of this study was to investigate the association between ultrasound findings and preterm infants with bronchopulmonary dysplasia (BPD).

Methods: Preterm infants with a gestation age of less than 28 weeks or birthweight less than 1,500 g admitted to the neonatal intensive care unit (NICU) in the Chengdu Women's & Children's Central Hospital from June 2018 to June 2019 were enrolled in the study and divided into 2 groups: the BPD group and the non-BPD group. All clinical data and lung ultrasound were retrospectively analyzed.

Results: A total of 81 neonates (gestational age =29.71±2.27 weeks; birth weight =1,189.5±184.5 g) were enrolled in our center. The regression analysis showed that gestational age [odds ratio (OR) =0.57; 95% confidence interval (CI): 0.42–0.77, P=0.0002], birthweight (OR =0.99; 95% CI: 0.99–1.00, P<0.0001), mild asphyxia (OR =3.3; 95% CI: 1.24–8.74, P=0.0165), anemia (OR =4.43; 95% CI: 1.34–14.64, P=0.0146), blood transfusion (OR =3.68; 95% CI: 1.38–9.79, P=0.0090), respiratory failure (OR =6.58; 95% CI: 1.27–34.08, P=0.0486), heart failure (OR =6.58; 95% CI: 1.27–34.08, P=0.0248), and “debris” lung ultrasound findings (OR =21.82; 95% CI: 2.63–181.11, P=0.0043) were correlated with BPD.

Conclusions: BPD-related lung ultrasound findings can be a kind of imaging marker to diagnose BPD.

Keywords: Preterm infants; ultrasound finding; bronchopulmonary dysplasia (BPD)

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Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common and severe respiratory diseases in preterm infants, especially those of extreme preterm birth and very low birthweight, and was thought to be a chronic progressive lung injury, along with pulmonary parenchyma and vascular changes (1). Compared to non-BPD children, children with BPD have a significantly higher risk of pulmonary dysfunction, speech impairment, cerebral palsy, hearing and vision impairment like in retinopathy of prematurity, and long-term cognitive dysfunction (2,3). BPD prevalence

varies widely across different countries, ranging from 10% to 89% worldwide. A study in China showed that BPD affects up to 82% of the population of infants with a gestation age from 24 to 28 weeks (4). The main reasons of this phenomenon include the different diagnostic criteria in studies, infants involved with different gestational ages and weights, and the various diagnosis and treatment strategies applied in different centers (5). Thus, it is very important to define the incidence of BPD, and to unify the diagnostic criteria and treatment strategies for the clinical management of very premature infants and the study of new

treatment options (3). Northway was first to describe the clinical manifestations of BPD and its typical X-ray findings in near-term infants in 1967 (6), but the lung X-ray findings are no longer used as a criterion for assessing the severity of BPD at present (7). There are many studies focusing on the clinical prediction models and biochemical predictors of BPD, but only a few studies on the changes in lung ultrasound images (8). In recent years, with the development of ultrasound diagnostic technology, the value of ultrasound in lung diseases has gradually been recognized, especially in the newborns (9). The study presented here investigated the diagnostic value of lung ultrasound findings in preterm infants with BPD.

Methods

Patients

We conducted a retrospective, single-center study of preterm infants. The data of preterm infants with a gestational age ≤ 28 weeks or a birth weight $\leq 1,500$ g, who were admitted to the Chengdu Women's and Children's Central Hospital, between June 2018 and June 2019, were collected.

Cases were excluded from analysis if the infants had congenital malformations (such as congenital heart disease, diaphragmatic hernia, pulmonary bulla, congenital cystic adenomatoid malformation of the lung (CCAM), craniocerebral malformation, etc.) or incomplete clinical data.

Methodology

The diagnostic criteria for BPD were infants with oxygen dependence (<0.21) 28 days after birth and a gestational age less than 32 weeks (10). According to fraction of inspiration (FiO_2) at 36 weeks' gestational age or at discharge, we divided BPD levels as follows: (I) mild, without oxygen; (II) moderate, $FiO_2 < 0.30$; (III) severe, requires $FiO_2 > 0.30$ and/or continuous positive airway pressure (CPAP), or mechanical ventilation.

Lung ultrasound was taken and read by 2 well-trained ultrasound surgeons during BPD routine ultrasound screening (Table 1). The machine used for lung ultrasound was the PHILIPS CX50 portable ultrasound diagnostic instrument, with linear array probe at a frequency of 12 to 13 MHz.

According to the lung ultrasound acquisition standard described in previous work (11), we developed the standard in our center. First, children were supine to check the anterior chest to see whether there was pneumothorax or other symptoms. Then, the scan was extended to the lateral chest to check whether there was pleural effusion or lung disease. Finally, patients lay in the lateral or prone position so the presence of pleural lesions and consolidation could be determined according to the pathogenetic condition. We distinguished pneumothorax, pleural effusion, pulmonary edema, pulmonary consolidation, atelectasis, and other disease according to the signs of pleural slip, A line, B line, lung point, bronchial inflation, and so on. Each side of the chest wall was divided into 6 sections based on the parasternal line, anterior axillary line, posterior axillary line, and extension line of double nipple, which included the anterior upper, lower anterior, lower axillary, upper axillary, posterior upper, and lower posterior sections, and recorded as L1-6 and R1-6 images, respectively. Cross-section and longitudinal-section audiograms were acquired and marked, and surface signs were labeled if necessary. We took at least 12 images in double-picture mode. Lung ultrasound was acquired once a week from 3 weeks after birth to discharge. Statistics were accumulated for abnormal changes in ultrasound findings. The specification of lung ultrasound diagnosis of BPD was listed as follows: (I) changes in pleural line such as interruption, disappearance, thinning, and thickening; (II) presence of B line which indicated fusion or alveolar interstitial syndrome (Figure 1); (III) a section of pulmonary consolidation with subpleural structure disorders, fragment-like strong echoes, and irregular weak echo areas visible below (Figure 2); (IV) pleural effusion; (V) radiographic evaluation of various complications, such as lung abscess; (VI) the presence of slippery lung syndrome.

Statistical analysis

Statistical analysis was performed using SPSS, version 19.0 (IBM Corp). The mean of normal distribution was assessed with measurement data presented as a percentage. The median (maximum and minimum) was estimated in non-normal distribution data. Factors such as gender, gestational age, birth weight, asphyxia, and complications were assigned to variables, and univariate analysis was performed to calculate the odds ratios (OR) and their 95% confidence intervals (CI). Logistic multiple regression analysis was performed on the multiple factors above to calculate OR

Table 1 Characteristics of infants in this study

Characteristics	BPD	Non-BPD	P value
Demographics	32	49	
Gestational age (week)	28.4±1.8	30.6±2.2	<0.001
Birth weight (g)	1,079.7±165.3	1,261.2±162.8	<0.001
Gender			0.704
Male	19 (59.4%)	27 (55.1%)	
Female	13 (40.6%)	22 (44.9%)	
Assisted reproductive technology (ART)			0.108
Yes	18 (56.2%)	36 (73.5%)	
No	14 (43.8%)	13 (26.5%)	
Born at hospital			0.013
No	7 (21.9%)	2 (4.1%)	
Yes	25 (78.1%)	47 (95.9%)	
Infection history during pregnancy			0.154
No	32 (100.0%)	46 (93.9%)	
Yes	0 (0.0%)	3 (6.1%)	
Premature rupture of membrane (PROM)			0.612
No	22 (68.8%)	31 (63.3%)	
Yes	10 (31.2%)	18 (36.7%)	
GBS colonization			0.213
No	31 (96.9%)	49 (100.0%)	
Yes	1 (3.1%)	0 (0.0%)	
Pregnancy complicating with hypertension			0.664
No	27 (84.4%)	43 (87.8%)	
Yes	5 (15.6%)	6 (12.2%)	
Cholestasis during pregnancy (ICP)			0.097
No	32 (100.0%)	45 (91.8%)	
Yes	0 (0.0%)	4 (8.2%)	
Pregnancy with diabetes			0.811
No	23 (71.9%)	34 (69.4%)	
Yes	9 (28.1%)	15 (30.6%)	
Prenatal hormone use			0.260
No	4 (12.5%)	11 (22.4%)	
Yes	28 (87.5%)	38 (77.6%)	
Prenatal application of MgSO ₄			0.314
No	24 (77.4%)	35 (71.4%)	
Yes	6 (19.4%)	14 (28.6%)	
Unknown	1 (3.2%)	0 (0.0%)	

BPD, bronchopulmonary dysplasia; GBS, *Streptococcus agalactiae*.

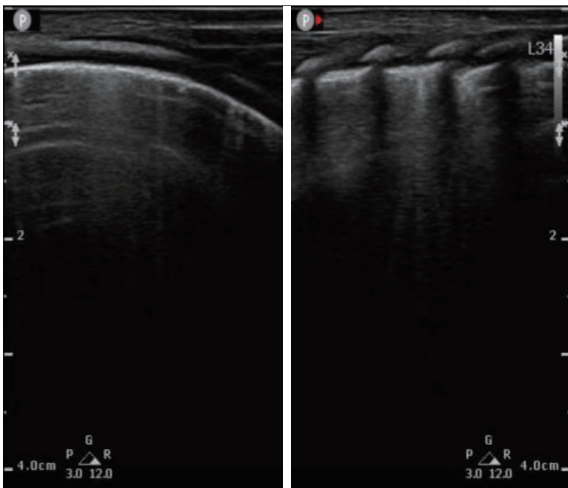


Figure 1 Lung ultrasound showed “alveolar interstitial syndrome” in BPD patients. BPD, bronchopulmonary dysplasia.

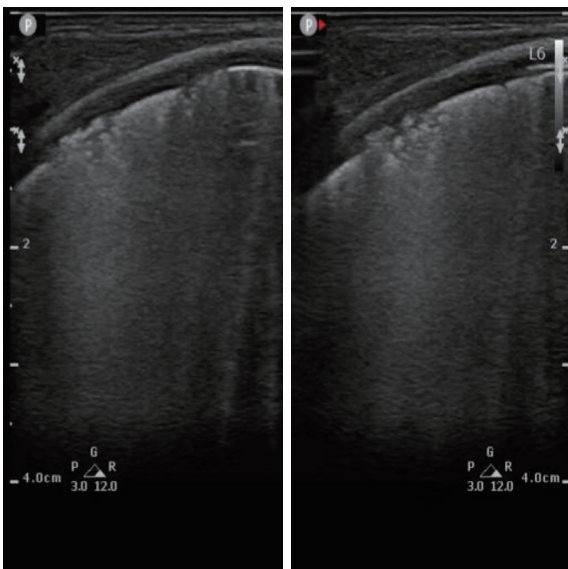


Figure 2 “Debris” lung ultrasound findings in BPD patients. BPD, bronchopulmonary dysplasia.

and its 95% CI. Results with $P < 0.05$ were considered statistically significant.

Results

Basic situation

In this study, the incidence of BPD was 39.5% among the enrolled 81 preterm infants (gestational age ≤ 28 weeks or birth weight $\leq 1,500$ g) from June 2018 to June 2019.

There were 46 male and 35 female infants, with an average gestational age of 29.71 ± 2.27 weeks and average birth weight of $1,189.5 \pm 184.5$ g. For BPD patients, the average hospitalization day was 58.8 days (Figure S1).

Single factor analysis of clinical high-risk factors in the BPD group and non-BPD group (Table 2)

The results indicated that the clinical risk was significantly different between the BPD group and non-BPD group children with a gestational age of 28.4 ± 1.8 weeks and a birth weight of $1,079.7 \pm 165.3$ g. The regression analysis showed that gestational age (OR = 0.57; 95% CI: 0.42–0.77, $P = 0.0002$), body weight (OR = 0.99; 95% CI: 0.99–1.00, $P < 0.0001$), mild asphyxia (OR = 3.3; 95% CI: 1.24–8.74, $P = 0.0165$), anemia (OR = 4.43; 95% CI: 1.34–14.64, $P = 0.0146$), blood transfusion (OR = 3.68; 95% CI: 1.38–9.79; $P = 0.0090$), respiratory failure (OR = 6.58; 95% CI: 1.27–34.08, $P = 0.0486$), and cardiac insufficiency (OR = 6.58; 95% CI: 1.27–34.08, $P = 0.0248$) were all clinical risk factors in BPD and showed significant difference compared to the non-BPD group.

Multivariate analysis of clinical data in the BPD group (Table 3)

Multivariate analysis of clinical data indicated that blood product (OR = 5.49; 95% CI: 0.042–0.791, $P = 0.023$) was independent high risk factor of BPD.

Univariate analysis lung ultrasound findings in the BPD group and non-BPD group

The ultrasound result indicated that presence of “debris” lung ultrasound findings (OR = 21.82; 95% CI: 2.63–181.11, $P = 0.0043$) was correlated with BPD and could be a high-risk factor for BPD (Table 4).

Discussion

Currently, the consensus BPD definition is the one proposed in 2000 by the National Institute of Child Health and Human Development (NICHD) (10) whose main diagnostic criterion was infants acknowledged to have been treated with oxygen for over 28 days and at 36 weeks' corrected age. Research indicates that assessment of oxygen dependence can be used to identify the mild, moderate, and severe categories of BDP, but is insufficient in predicting

Table 2 Single factor analysis of clinical high-risk factors between the BPD group and non-BPD group

Variable	BPD	Non-BPD	P value	OR, 95% CI	P value
Female	22 (44.9%)	13 (40.6%)	0.704	0.84 (0.34, 2.07)	0.7044
Gestational age (week)	28.4±1.8	30.6±2.2	<0.001	0.57 (0.42, 0.77)	0.0002
Birth weight (g)	1,079.7±165.3	1,261.2±162.8	<0.001	0.99 (0.99, 1.00)	<0.0001
Assisted reproductive technology (ART)	13 (26.5%)	14 (43.8%)	0.108	2.15 (0.84, 5.53)	0.1109
Premature rupture of membrane (PROM)	18 (36.7%)	10 (31.2%)	0.612	0.78 (0.30, 2.02)	0.6122
Pregnancy complicating with hypertension	6 (12.2%)	5 (15.6%)	0.664	1.33 (0.37, 4.78)	0.6649
Pregnancy with diabetes	15 (30.6%)	9 (28.1%)	0.796	0.89 (0.33, 2.37)	0.8106
Prenatal hormone use	38 (77.6%)	28 (87.5%)	0.260	2.03 (0.58, 7.03)	0.2659
Prenatal application of MgSO ₄	14 (28.6%)	6 (19.4%)	0.314	0.63 (0.21, 1.86)	0.3973
Postnatal asphyxia			0.020		
Mild	15 (30.6%)	17 (53.1%)		3.30 (1.24, 8.74)	0.0165
Severe	2 (4.1%)	4 (12.5%)		5.82 (0.93, 36.29)	0.0593
Caffeine use	24 (75%)	23 (47%)	0.017	8.97 (1.10, 73.32)	0.0406
Postnatal blood transfusion	24 (75%)	21 (43%)	0.004	3.68 (1.38, 9.79)	0.0090
Alveolar surfactant use	26 (81%)	35 (71%)	0.316	1.61 (0.54, 4.80)	0.3931
Azithromycin use	6 (19%)	6 (12%)	0.420	1.65 (0.48, 5.67)	0.4235
Heart failure	7 (22%)	2 (4%)	0.013	6.58 (1.27, 34.08)	0.0248
Respiratory failure	30 (94%)	37 (76%)	0.034	4.86 (1.01, 23.44)	0.0486
NRDS	29 (91%)	34 (69%)	0.025	4.26 (1.12, 16.20)	0.0332
Congenital heart disease	20 (63%)	25 (51%)	0.309	1.60 (0.64, 3.97)	0.3108
Pneumorrhagia	4 (13%)	3 (6%)	0.318	2.19 (0.46, 10.52)	0.3273
Anemia	28 (88%)	30 (61%)	0.010	4.43 (1.34, 14.64)	0.0146
GRED	9 (28%)	9 (18%)	0.302	1.74 (0.60, 5.00)	0.3047
NEC	5 (16%)	10 (20%)	0.588	0.72 (0.22, 2.35)	0.5889
IVH	16 (50%)	8 (16%)	0.001		
I	10	5		5.13 (1.64, 15.99)	0.0049
II	2	1		2.56 (0.15, 43.48)	0.5148
III	2	1		2.56 (0.15, 43.48)	0.5148
IV	2	1		Inf. (0.00, Inf)	0.9918
Septicemia	9 (28%)	10 (20%)	0.423	1.53 (0.54, 4.31)	0.4246
Premature infant encephalopathy	20 (63%)	20 (41%)	0.056	2.42 (0.97, 6.03)	0.0587
ROP	21 (66%)	20 (41%)	0.029	2.77 (1.10, 6.99)	0.0311

BPD, bronchopulmonary dysplasia; NRDS, neonatal respiratory distress syndrome; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; GRED, gastroesophageal reflux disease; OR, odds ratio; CI, confidence interval.

Table 3 Multivariate analysis of clinical data of BPD

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Respiratory failure	-0.693	1.384	0.251	1	0.617	0.500	0.033	7.541
Heart failure	-0.847	0.959	0.780	1	0.377	0.429	0.065	2.810
NRDS	0.288	1.607	0.032	1	0.858	1.333	0.057	31.121
Anemia	-1.030	1.222	0.710	1	0.399	0.357	0.033	3.916
blood products	-1.705	0.75	5.161	1	0.023	0.182	0.042	0.791
IVH	-1.281	0.749	2.924	1	0.087	0.278	0.064	1.206
ROP	0.519	0.725	0.512	1	0.474	1.680	0.405	6.962

BPD, bronchopulmonary dysplasia; NRDS, neonatal respiratory distress syndrome; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.

Table 4 Analysis of lung ultrasound findings in the BPD group and non-BPD group

Variable	BPD (n=32)	Non-BPD (n=49)	P	OR, 95% CI	P
Sum	32	49			
A line (decrease/disappear)	25 (78%)	31 (63%)	0.005	2.52 (0.87, 7.27)	0.0882
B line (scattered/fused/dense)	32 (100%)	46 (94%)	0.008	–	–
Pleural line (thickened, interrupted)	31 (97%)	39 (80%)	0.026	7.95 (0.96, 65.48)	0.0540
Air bronchogram	10 (31%)	9 (18%)	0.181	2.02 (0.71, 5.72)	0.1851
Fragment consolidation	10 (31%)	1 (2%)	0.001	21.82 (2.63, 181.10)	0.0043
Patchy consolidation	10 (31%)	12 (24%)	0.504	1.77 (0.64, 4.92)	0.2715
Layered consolidation	5 (16%)	4 (8%)	0.296	1.63 (0.43, 6.16)	0.9912

BPD, bronchopulmonary dysplasia; OR, odds ratio; CI, confidence interval.

risks for adverse neurodevelopmental outcomes that occur during follow-up (12). Studies on BPD from the past 50 years suggest that BPD is mainly caused by mechanical ventilation injury in the near full-term infants at the early stage, while a new kind of BDP often occurs in infants ≤ 28 weeks' gestational age, with or without mild lung disease at birth, and with no oxygen or low-oxygen treatment being required. However, oxygen dependence gradually develops during hospitalization, with symptoms such as alveolar hypoplasia, disturbance of vascular development, fibrosis of the vesicle wall, and small airway epithelium injury, along with histopathological changes such as reduced alveolar number, increased alveolar volume, simplified alveolar structure, and abnormal microvascular morphology (7,13). Even the cure rate for premature infants is increasing, but the incidence of BPD varies in clinical studies due to the

lack of uniform diagnostic criteria (5). According to the study by the NICHD, the incidence of BPD was 39.5% in the group of 81 infants (gestational age ≤ 28 weeks, birth weight $\leq 1,500$ g), which is quite similar to the recent data in China (14).

In our study, the gestational age of BPD was mainly at 28 weeks and with few very premature infants, so it cannot be further analyzed based on different gestational ages. Although we have developed many imaging diagnostic techniques, such as chest radiography, lung computed tomography (CT), lung ultrasound, and lung magnetic resonance imaging (MRI) (15,16), there are few reports discussing the value of different BPD imaging diagnoses (8). Here, we used lung ultrasound technology to test the changes in lung images for infants (gestational age ≤ 28 weeks, birth weight $\leq 1,500$ g) and discovered that

lung ultrasound findings with “debris” sign could be an independent risk factor for BPD disease. Furthermore, due to the advantages of emitting no radiation, being portable, providing convenient bedside monitoring, and being easy to grasp by clinicians, lung ultrasound could be widely used in clinical work (17). A study by Avni *et al.* showed that infants with ultrasound sonographic images similar to hyaline membrane disease (HMD) had a negative predictive value of 95% for BPD assessment in the future (18). A similar study indicated that sonographic results on the ninth day after birth also had a prediction of BPD in the long term (19), while other research found that lung ultrasound scores can predict the occurrence of BPD within 1–2 weeks of birth (20). Reviewing 26 clinical prediction models for BPD, Onland *et al.* found that the risk factors and multiple diagnostic models for predicting BPD proposed in the current study are of low diagnostic value [area under the curve of the receiver operating characteristic curve (AUC of ROC) =0.5–0.76]. Moreover, these prediction models had not been applied in clinical work, and little research had confirmed further whether these models’ application could improve clinical decision or affect prognosis (21). Most of these investigations focused on the prediction of gestational age, birth weight, gender, Apgar score, mean oxygen concentration, maximum oxygen concentration, peak inspiratory pressure, and oxygenation index, but did not mention image changes in the diagnosis value of BPD. Therefore, our present study focused on ultrasound application in BPD diagnosis and found that the BPD-related lung ultrasound findings can be further used as a reference for BPD diagnosis, and may also provide a means to identify lung lesions in the early stage.

Limitations of this study may include the small sample size, the small number of special ultrasound signs, and no specific analysis on the occurrence time of characteristic ultrasound images. At present, there is still a controversy over the standardization and quality control of lung ultrasound images, and thus more clinical research to make standardized image acquisition and reading specifications is required.

Ultrasound, an auxiliary diagnostic method for lung diseases, is widely reported to have the advantages of a lack of radiation, simple operation, and easy follow-up. In this study, we deepened the understanding of the characteristic lung ultrasound findings for BPD through analyzing numerous ultrasonic images of very premature infants. We hope this research can facilitate further exploration into the diagnosis and prediction of BPD in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tp.2020.03.14>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Ethics Committee of Chengdu Women’s and Children’s Central Hospital [No. 2019(37)].

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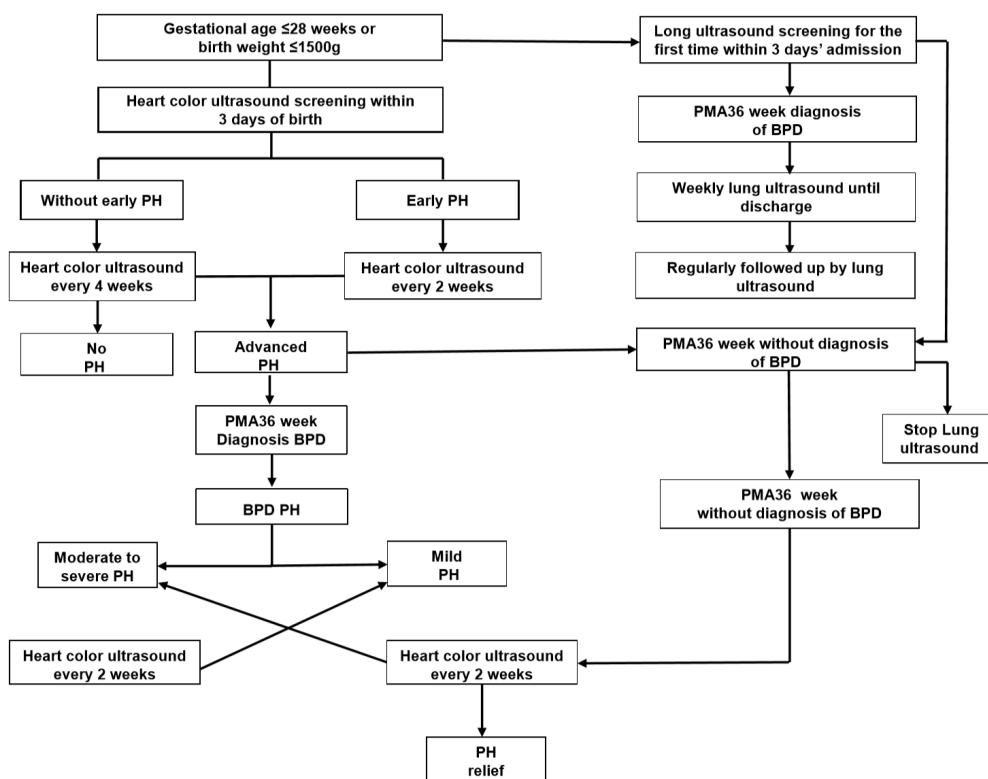


Figure S1 Flow chart of lung ultrasound and heart color ultrasound screening. BPD, bronchopulmonary dysplasia.