European Review for Medical and Pharmacological Sciences 2023; 27: 5964-5972

Application of lung ultrasound in monitoring bronchopulmonary dysplasia and pulmonary arterial pressure in preterm infants

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the application value of lung ultrasound in monitoring bronchopulmonary dysplasia (BPD) and pulmonary artery pressure in premature infants.

PATIENTS AND METHODS: A total of 98 preterm infants diagnosed with BPD in the Fourth Hospital in Shijiazhuang were recruited, and their disease severity was classified as mild (n=32), moderate (n=33), or severe BPD (n=33) based on gestational age and oxygen concentration. Lung ultrasonography of the children was performed. The correlation between lung ventilation scores and disease severity was statistically analyzed, and the discrete optimization results were documented. The pulmonary hypertension indexes of the three groups of children were compared.

RESULTS: Aberrant alterations of the pleural line were observed in all included children, and the B-line rose as the disease progressed. The duration of invasive ventilation, medication, and hospital stay increased with disease exacerbation ($p<0.05$). The three groups significantly differed in terms of ultrasound pulmonary ventilation scores and clinical severity ($p<0.05$). Only mild BDP was identified by lung ultrasound on the first day of birth (T1), and severe BDP was detectable during the first and second week (T2-T3) as well as the third and fourth week (T4-T5). Severe BPD was associated with significantly higher levels of pulmonary hypertension indices vs. mild and moderate BPD ($p<0.05$).

CONCLUSIONS: Pulmonary ultrasonography demonstrates great potential to predict pulmonary hypertension in children and assesses the disease severity. Pulmonary ultrasound allows for dynamical real-time observation of the pulmonary lesions in children with pulmonary hypertension, thereby revealing the severity of pulmonary hypertension in premature children.

Key Words:
Pulmonary ultrasound, Premature infants, Bronchopulmonary dysplasia, Pulmonary artery pressure, Lung ventilation.

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory disease in preterm infants. In recent years, the prevalence of BPD has shown an increasing trend. Reportedly[1], at least one-quarter of preterm infants with a birth weight of less than 1,500 g suffer from BPD, and the incidence of BPD increases as the gestational age and birth weight of preterm infants decrease. BPD is also associated with a high mortality rate, with research[2] revealing a 5% mortality rate in children with mild BPD and 19% in children with moderate to severe BPD. In addition, preterm infants with BPD are predisposed to developmental delay, pneumonia, and wheezing after hospital discharge[3], resulting in poor survival and prognosis.

Abnormal pulmonary artery pressure is another leading cause of child mortality. Abnormal pulmonary artery pressure, also known as exercise-induced pulmonary hypertension (PH), is associated with reduced aerobic capacity and compromised right ventricular systolic function[4]. BPD causes damage to the alveoli and the surrounding blood vessels, and long-term BPD may lead to cardiac impairment. Currently, the elevating prevalence of BPD constitutes one of the most pressing issues in the neonatal intensive care unit (NICU)[5,6].

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Current disease management for BPD includes breastfeeding, respiratory support, glucocorticoids, and azithromycin. Nevertheless, highly effective BPD treatment protocols are clinically unavailable. It is worth noting that traditional Chinese medicine (TCM) has shown features favoring the enhancement of cardiac and other organ functions[7]. Zheng et al[8] have found that Shashen Maidong Decoction has immunosuppressive effects. Ophiopogon japonicus in the recipe contains saponins, alkaloids, sitosterol, glucose, amino acids and vitamins, providing functions of anti-fatigue and scavenging free radicals. Combined with northern ginseng, it could enhance the effect of tonifying lung yin, and the addition of mulberry leaves and other components in the prescription enhances the efficacy of anti-inflammation and free radical scavenging. Different doses of Shashen Maidong decoction can obviously reverse the pathological changes of rat lung tissue caused by hyperoxia, reduce the secretion of inflammatory factors, and significantly mitigate the severity of pulmonary edema in rats.

In 1967, Northway[9] first described the clinical presentation and typical pulmonary radiographic manifestations of BPD in preterm infants, but the typical pulmonary radiographic manifestations have now been excluded as a diagnostic criterion[10]. At present, the diagnosis of BPD is mainly based on clinical oxygen dependence, with auxiliary imaging methods such as X-ray and chest computerized tomography (CT)[11,12]. However, chest X-ray is inaccurate in displaying mild lesions, and chest CT is unavailable for critically ill children[13,14]. Higano et al[15] have been performed mostly on clinical prediction models and biochemical predictors of BPD occurrence, but few focused on pulmonary ultrasound imaging alterations of BPD. With the development of diagnostic ultrasound technology, the role of pulmonary ultrasound in lung disease diagnosis, especially in neonatal diseases, has been gradually recognized[16]. Children with BPD with secondary PH exhibit non-specific symptoms and signs resembling those seen with severe BPD, which complicates the diagnosis and underlines the necessity of PH screening prior to BPD diagnosis[17,18].

Children with BPD are prone to structural and functional pulmonary abnormalities and increased pulmonary vascular resistance due to abnormal development of the vascular bed and pulmonary vascular remodeling[19,20]. PH is one of the major causative factors for the high prevalence and mortality of pediatric BPD[21]. Furthermore, a previous study[22] found an association between pulmonary ventilation and the disease severity of the children. To this end, the purpose of this study is to evaluate the application value of lung ultrasound in monitoring BPD and pulmonary artery pressure in premature infants.

Patients and Methods

Participants

Between March 2020 and March 2022, 98 preterm infants diagnosed with BPD in the Fourth Hospital in Shijiazhuang were recruited and classified as mild (n=32), moderate (n=33), or severe BPD (n=33) based on gestational age and oxygen concentration. Undersigned informed consent was obtained from patients' guardians prior to enrollment in this study.

The original sample size calculation estimated that 30 patients in each group would be needed to detect a 3-point difference between groups in a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

This was a prospective cohort study. The study protocol was approved by the ethics committee of Shijiazhuang's Fourth Hospital, approval No. 39797-51. The study conformed to the Declaration of Helsinki ethical guidelines for clinical research[21]. The technical roadmap of this study is shown in Figure 1.

Inclusion Criteria and Exclusion Criteria

Inclusion criteria

Children with a gestational age of less than 37 weeks, clinically diagnosed BPD, and survival

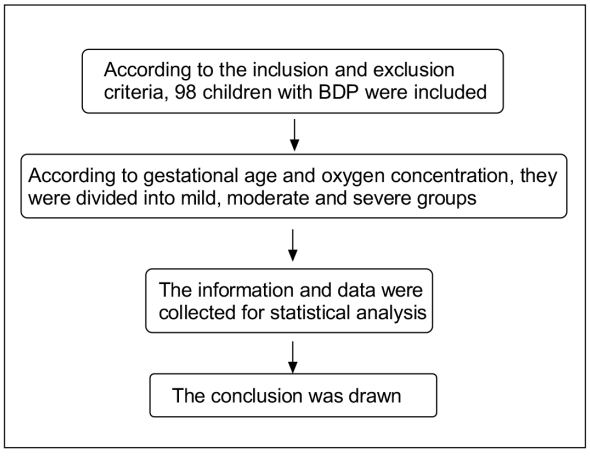

Figure 1. Technical roadmap.

of over 28 days, were included. Diagnosis criteria of BPD: newborn with oxygen dependency (>21%) for more than 28 days, such as gestational age <32 weeks, was classified based on the corrected gestational age of 36 weeks or oxygen requirement at discharge as (1) mild: no oxygen; (2) moderate: FiO_2 <30%; (3) severe: FiO_2 ≥30% or requiring mechanical ventilation. If the gestational age ≥32 weeks, according to the degree of oxygen requirement at 56 days after birth or at the time of discharge, they were classified as mild, moderate, or severe as above.

Exclusion criteria

Children who died within 36 weeks of age, with severe thoracic deformities, tumors, and chromosomal diseases, with congenital heart disease other than Patent Ductus Arteriosus (PDA) and Atrial Septal Defect (ASD), or with dysplasia of the large airways, history of cardiopulmonary surgery, severe lung infection, severe primary pulmonary hypertension, and other interstitial lung diseases were excluded.

Method

The examination was performed with the children in a supine or lateral position in a quiet state. With the front axillary line and the back axillary line as the boundary, the lungs were radiographically divided into 3 areas, namely, front, side, and back areas, totaling 6 scanning areas on both sides. A diagnostic color ultrasound machine was used (Hitachi Aloka Medical Ltd, Tokyo, Japan) was used for the lung ultrasound examination. The examination was performed by a specialist sonographer and the six scanning areas of the children were rated. A linear array probe with a frequency of 5-10 MHz was used.

Observation Indicators

The ultrasound performance of the children's lungs was observed. The scoring criteria for lung ultrasound are as follows.

1. Normal zone: if the number of B-lines in the scan plane is ≤3, it is scored 0 points.
2. Mild humidity zone: if the number of B-lines in a scanning plane is 4-6, it is scored 1 point.
3. Moderate humidity zone: if the number of B-line >6 or B-line merges small fragments in a scanning plane, it is scored 2 point.;
4. Severe humidity zone: if there is no A-line, and B-line in one scanning plane but a waterfall sign, and it is scored 3 points.

Lung tissue consolidation: the maximum diameter of the consolidation less than 10 mm is scored 4 points, between 10 mm and 20 mm is scored 5 points, and over 20 mm is scored 6 points. The ultrasound score of the children is the sum of 6 lung area scores, with a full score of 0-36 points.

The first day, first week, second week, third week, and fourth week after the child's birth were set as T1, T2, T3, T4, and T5, and the correlation between ultrasound lung ventilation scores at different time points of the children with BPD and severity of the disease was statistically analyzed.

The discrete optimization results at different time points were analyzed. The pulmonary hypertension indexes of the three groups of children were compared.

Statistical Analysis

The normality of the sample was determined with the Shapiro-Wilk test. Descriptive statistical data were evaluated with the exploratory analyses of the Tukey test. Quantitative mean data (PES/WES, ISQ, and B.L.) were assessed with the nonparametric Wilcoxon-Mann-Whitney U test to analyze the inferential statistical.

The SPSS 21.0 software (IBM Corp., Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software, San Diego, USA) were employed for data analyses and graphic plotting, respectively. The enumerated data and measurement data were examined by χ^2 test and *t*-test, and expressed as [n (%)] and (). $p<0.05$ was considered as statistically significant.

Results

Patient Characteristics

The two groups were well-balanced in gestational age, gender, birth weight, or place of residency between the three groups of children ($p>0.05$), but the duration of invasive ventilation, medication time, and hospitalization time increased as the disease deteriorated ($p<0.05$) (Table I).

Ultrasound Performance

Aberrant alterations of the pleural line were observed in all included children, and the B-line rose as the disease progressed (Figures 2 and 3).

Table I. Comparison of general information of the three groups of children.

	Mild group (N = 32)	Moderate group (N = 33)	Severe group (N = 33)	χ^2/t	p
Gestational week (week)	40.37 ± 2.32	40.11 ± 2.45	40.23 ± 2.38	0.294	0.771
Gender				0.081	0.870
Male	17	18	17		
Female	15	15	16		
BMI at birth (g)	1,233.84 ± 217.62	1,237.88 ± 220.35	1,241.51 ± 216.76	0.094	0.925
Invasive ventilation time (d)	2.11 ± 2.78	7.53 ± 5.88	17.35 ± 8.74	6.594	< 0.001
Oxygen time (d)	40.21 ± 7.98	55.36 ± 9.51	65.78 ± 20.02	6.947	< 0.001
Hospital stay (d)	49.81 ± 8.77	59.62 ± 8.92	75.33 ± 18.25	7.129	< 0.001
Places of residence				0.142	0.741
City	20 (66.67)	19 (70.00)	21 (73.33)		
Rural area	12 (33.33)	14 (30.00)	12 (26.67)		

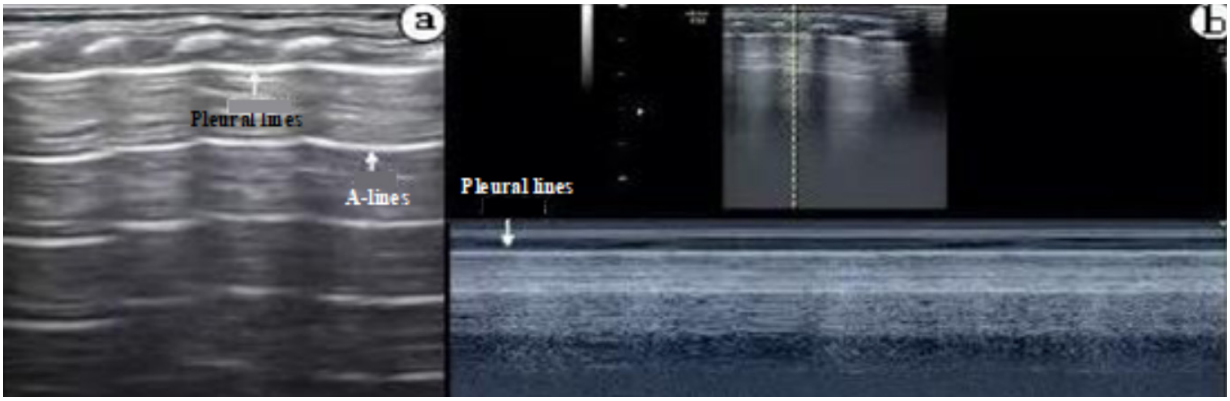

Figure 2. Ultrasound manifestations of neonatal normal lungs. **a**, Ultrasound clearly shows the A-lines and the pleural lines, and the two are arranged in parallel at equal intervals, which is called the "Slub sign". **b**, Pleural line is line-like hyperechoic above and below the uniform particle-like spots produced by lung slip. The shape of a high echo is called a "Beach sign".

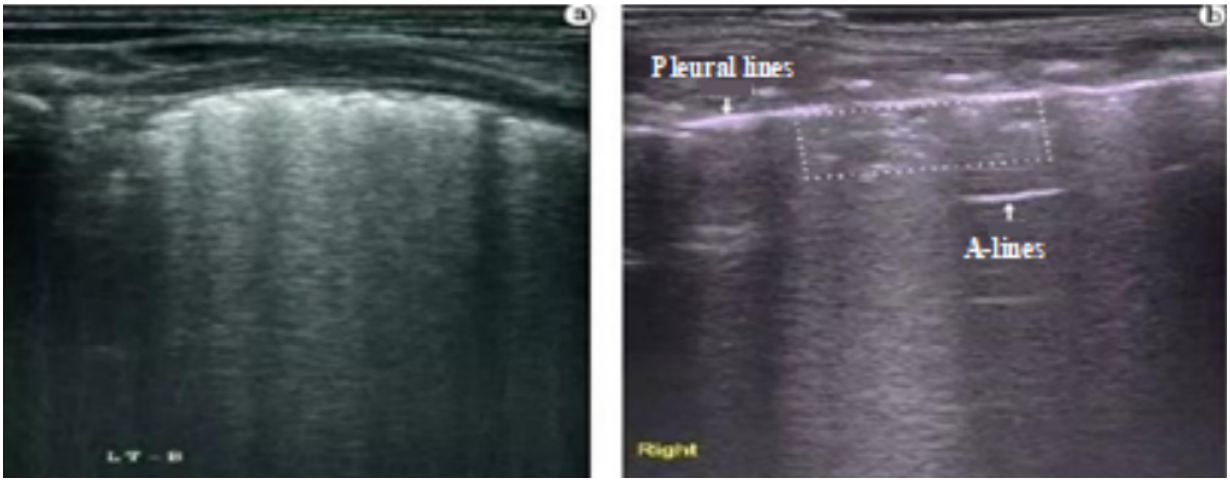

Figure 3. Ultrasound imaging manifestations of severe BDP. **a**, Abnormal pleural line: clinical diagnosis of BDP, LUS shows abnormal thoracic pattern line, with dense B-line. **b**, Vesicle inflation sign: LUS shows that the thoracic pattern line is thickened and blurred, with more B-lines, scattered in the dotted area, and dotted hyperechoic emission was observed in a dotted area.

Table II. Comparison of ultrasound lung ventilation scores at different time points and clinical severity ($\bar{x} \pm s$).

	N	T1	T2	T3	T4	T5
Mild group	32	8.01 ± 3.59	8.05 ± 3.61	7.85 ± 3.51	6.11 ± 2.98	4.88 ± 2.75
Moderate group	33	10.47 ± 5.39*#	10.87 ± 5.41	10.22 ± 4.65	9.75 ± 4.01	8.82 ± 3.97
Severe group	33	14.05 ± 5.88	14.15 ± 5.65	13.99 ± 5.27	14.07 ± 4.05	14.04 ± 4.02

*Represents significant differences ($p < 0.05$) when compared with the mild group; #Represents significant differences ($p < 0.05$) when compared with the severe group.

Table III. The optimal discretization results of lung ultrasound scores at different time points and different degrees of disease.

	Cutoff value	Mild group	Moderate group	Severe group	Total cases
Ultrasound scoring T1	< 14	32	26	10	68
	≥ 14	0	7	23	30
Ultrasound scoring T2	< 9	20	13	0	33
	≥ 9	12	20	33	65
Ultrasound scoring T3	< 10	22	11	0	33
	≥ 10	10	22	33	65
Ultrasound scoring T4	< 11	25	23	4	52
	≥ 11	7	10	29	46
Ultrasound scoring T5	< 10	29	26	3	58
	≥ 10	4	7	30	41

Comparison of Ultrasound Pulmonary Ventilation Score at Different Time Points and Clinical Severity

In terms of ultrasonography pulmonary ventilation score and clinical severity, the three groups differed significantly ($p<0.05$) (Table II).

Correlation between Ultrasound Pulmonary Ventilation Score and Clinical Severity at Different Time Points

The duration of invasive ventilation, medication, and hospital stay increased with disease exacerbation ($p<0.05$) (Figure 4).

The Discrete Optimization Results of Lung Ultrasound Scores and Different Degrees of Severity at Different Time Points

Only mild BDP was identified by lung ultrasound at T1, and severe BDP was detectable during T2-T3 as well as T4-T5 (Table III).

Comparison of the Pulmonary Artery Systolic Blood Pressure Indexes of the Three Groups of Children

Severe BPD was associated with significantly higher levels of pulmonary hypertension indices *vs*. mild and moderate BPD ($p<0.05$) (Figure 5).

Discussion

Bronchopulmonary dysplasia (BPD) is a chronic lung disease common in premature infants, especially in low birth weight neonates. The results of the present study revealed that lung ultrasound identifies all mild BPD at T1, most severe BPD

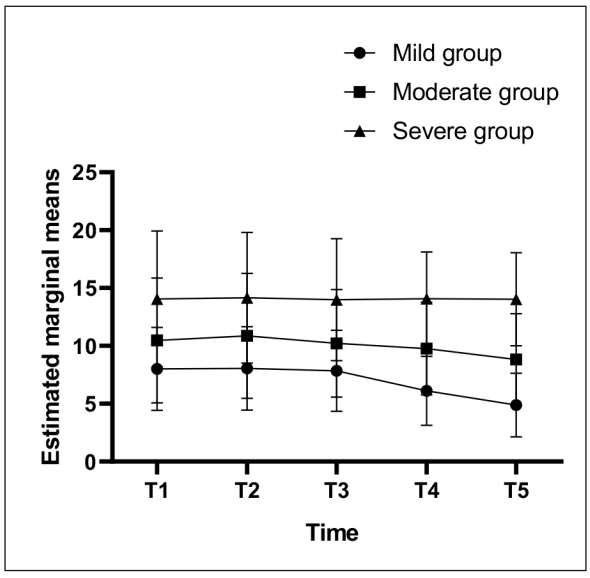

Figure 4. Correlation between ultrasound lung ventilation score at different time points and clinical severity ($\bar{x} \pm s$).

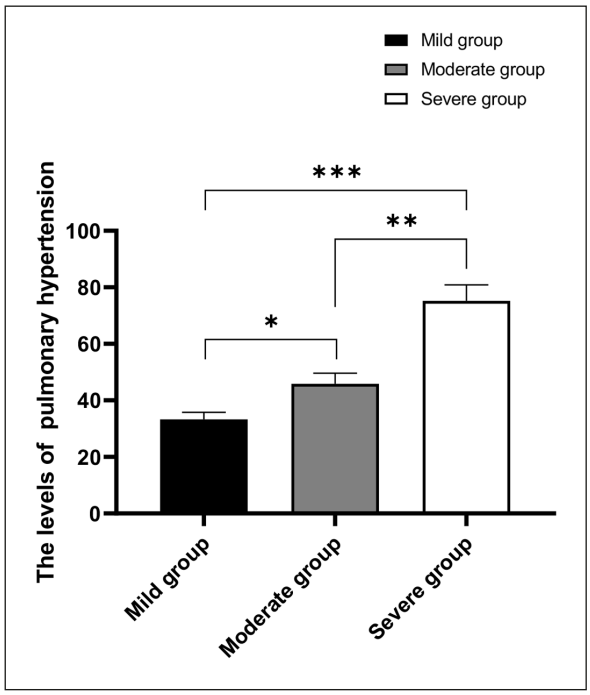

Figure 5. Comparison of the pulmonary artery systolic blood pressure indexes of the three groups of children ($\bar{x} \pm s$). The levels of pulmonary hypertension in the mild, moderate, and severe groups were (33.27±2.51) mmHg, (45.86±3.76) mmHg, and (75.22±5.69) mmHg, respectively. *Indicates that there is a significant difference between the mild group and the moderate group of pulmonary hypertension (t=17.083, $p < 0.001$); **Indicates that there is a significant difference in pulmonary hypertension between the low-concentration group and the high-concentration group (t=26.415, $p < 0.001$); ***Means that there is a significant difference between the middle-concentration group and the high-concentration group in pulmonary hypertension (t=40.069, $p < 0.001$).

at T1-T2, and all BPD at T3-T4. This result indicated that the lung ultrasound score demonstrates a good efficiency in distinguishing severe BPD. Moreover, the results also reported distinctively higher pulmonary hypertension in the severe group relative to the mild group and the moderate group, and this result is in line with the results of the study by Rinaldi et al[23] who stated that pulmonary artery pressure (77.81±6.33) mmHg in group C was remarkably higher than (30.11±2.49) mmHg and (50.88±3.21) mmHg in groups A and B, respectively. This suggests that the severity of BPD is positively correlated with pulmonary hypertension, and pulmonary ultrasound contributes to determining the condition of children with BPD, thereby providing reliable data for future treatment.

The clinical diagnosis of BPD is mainly based on the oxygen concentration required for oxygen-dependent preterm infants with 36 gestational weeks, and BPD prediction relies on birth weight, gestational age, and respiratory system severity[24,25]. However, this method fails to deliver a timely and accurate diagnosis of moderate to severe BPD[26-28]. Additionally, chest CT examination is discouraged for children with early disease and mild disease due to radiation concerns[29,30]. Lung ultrasound has assumed an important role in the diagnosis, differential diagnosis, and management of neonatal lung disease, and several international or national expert consensus or guidelines were established. Lung ultrasonography is radiation-free, non-invasive, and can be operated at the bedside, which is simple and easy to perform. The anterior, lateral, and posterior multi-position examination of lung ultrasound better make up for the lack of poor visualization of lesions on chest X-ray. Therefore, lung ultrasonography may outperform chest X-ray in the detection and diagnosis of occult atelectasis and small pulmonary consolidation.

The lung pathological changes of children with early BPD and mild BPD were mainly Inflammatory edema and consolidation. The detection rate of pulmonary edema and subpleural consolidation by ultrasound was not significantly different from that by chest CT. Therefore, lung ultrasound has definite advantages in evaluating the severity of lesions in children with early and mild BPD[31]. The chest X-ray or CT imaging manifestation of children with BPD is diverse, with different imaging features with pathological changes in different periods[32,33]. The reason may be the insufficient understanding of the pathophysiological mechanisms of BPD, which has led to inconsistent diagnostic criteria for the same group of cases[34,35].

Herein, the lung ventilation score is significantly correlated with the severity of the disease, so dynamic real-time follow-up is necessitated in clinical practice to detect children's lung ventilation and pulmonary artery pressure. It has been shown that lung ultrasound scores serve as a new auxiliary detection method, as it effectively predicts the occurrence of premature infants with BDP and the risk of pulmonary hypertension[36]. The ultrasound lung ventilation is distinct in the three groups of patients at T1-T5 in the present study, and the lung ventilation score increases with the severity of the disease. This result showed that the longer the mechanical ventilation duration, the more serious is the patient's

condition. It is presumably attributed to the fact that ventilator-associated pneumonia, oxidative damage, and pulmonary oxygen poisoning are associated with the pathogenesis of BPD, and prolonged mechanical ventilation triggers inflammatory reactions, which damage the children's pulmonary blood vessels and airways and worsens their condition. Ultrasonography provides more diagnostic benefits than chest X-ray as it offers dynamic observation and clearer images of lesions and has no radiation. Focal uneven ventilation and vesicular opacity are the more specific radiographic changes in moderate to severe BPD and undetectable by ultrasound imaging. In the present study, the lung ultrasound ventilation score was significantly correlated with the clinical severity, and the degree of oxygen dependence is closely related. The lung ultrasound score can be used for the dynamic follow-up observation in the clinical treatment of BPD children, to evaluate the prognosis of children and guide clinical practice. At present, there are studies[37,38] on the ultrasound diagnosis of adult interstitial lung diseases, and the ultrasound diagnosis of various pulmonary interstitial lesions in children may be the direction of further research. The results of this study indicate that pulmonary ultrasound has important clinical significance and potential in predicting and evaluating PH and predicting its severity in children, and can be used in clinical decision-making in the future.

Limitations

However, there are some limitations in this study. (1) In the application of ultrasound for the diagnosis of BPD, although the image acquisition is independent of report reading, the subjective nature of interpretation and the influence of clinical information may lead to selection and measurement bias. (2) This study only discussed the diagnostic value of lung ultrasound for BPD, but did not investigate its correlation with clinical features (such as the degree of lung lesions). (3) There is still controversy about the standardization and quality control of lung ultrasound images, therefore, it is necessary to unify the relevant diagnostic criteria.

Conclusions

Pulmonary ultrasonography demonstrates great potential to predict pulmonary hypertension in children and to assess the disease severity. However, diagnosis of BPD still requires the patient's medical history and biochemical tests to differentiate BPD from other neonatal interstitial lung diseases. If necessary, radiological examinations can be incorporated to further clarify the ventilation status of the lung tissue and is the presence of abnormality in airway development. Transthoracic and lung ultrasound feature no radiation, simple operation, dynamic observation, and good reproducibility.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Thanks to all researchers and subjects for their strong support of this clinical study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Informed Consent

All patients' guardians included in the study signed informed consent. All authors have read this manuscript and agreed to publish it.

Authors' Contribution

Y. Wang, M. Zhang and X.-Y. An designed the study and developed the research questions. Y. Wang, Y.-P. Tan, L. Zhang and L.N. Zheng performed the experiments and collected the data. Y. Wang, Y.-P. Tan, L.-P. Han and Y. Cui analyzed the data and conducted statistical analyses. J. Xie, L.-P. Han, Y. Wang and Y.-P. Tan wrote the paper and prepared the figures and tables.

Ethics Approval

The study protocol was approved by the ethics committee of Shijiazhuang's Fourth Hospital, approval No. 39797-51. The study conformed to the Declaration of Helsinki ethical guidelines for clinical research.

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