Analysis of the value of echocardiographic parameters in the early diagnosis of preterm infants with bronchopulmonary dysplasia

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Abstract. – OBJECTIVE: The objective of this study was to investigate the role of echocardiographic parameters in diagnosing bronchopulmonary dysplasia (BPD) in preterm infants.

PATIENTS AND METHODS: Ninety preterm infants with a gestational age of less than 32 weeks and a weight less than 1.5 kg, admitted to the neonatal intensive care unit of the hospital between January 2020 and January 2021, were selected for the study. The study subjects were divided into two groups: a BPD group (54 cases, observation group) and a non-BPD group (36 cases, control group). The correlation between tricuspid regurgitation (TR) velocity and BPD was investigated by detecting the cardiac function of preterm infants in both groups using a color Doppler ultrasound diagnostic instrument and analyzing the cardiac ultrasound results. The early prediction efficiency of TR velocity (m/s) for BPD was evaluated using the receiver operator characteristic (ROC) curve.

RESULTS: The incidence of patent ductus arteriosus (PDA) and pulmonary hypertension (PH) in the observation group was significantly higher than that in the control group. The levels of left ventricular ejection fraction (LVEF) and left ventricular shorting fraction (LVFS) were significantly lower than those in the control group ($p < 0.05$). The incidence of patent foramen ovale (PFO), atrial septal defect (ASD), and ventricular septal defect (VSD) in the observation group were not significantly different from the control group ($p > 0.05$). The proportion of tricuspid regurgitation in the observation group was significantly higher than that in the control group, and the TR velocity was significantly higher than that in the control group. The Spearman correlation analysis showed that TR velocity (m/s) was positively correlated to BPD severity ($r = 0.379$, $p < 0.05$). The area under the curve (AUC) for predicting BPD with TR velocity was 0.735. The sensitivity and specificity were 88.0% and 62.6%, respectively, when the TR velocity was 1.45 m/s.

CONCLUSIONS: Echocardiography is useful for understanding the degree of impaired cardiac function in preterm infants and for early detection of PH, which may reduce the mortality rate to a certain extent. The risk of BPD is significantly increased when TR velocity is higher than 1.45 m/s.

Key Words:
Bronchopulmonary dysplasia, Echocardiography, Pulmonary hypertension, Cardiac function.

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common and serious complications in preterm infants[1,2]. In recent years, with the full liberalization of China's second-child policy, the development of assisted reproduction technology, and the increase of elderly pregnant women, the incidence of preterm infants has been increasing year by year, and studies have shown that preterm infants currently account for about 9.9% of newborns in China, which is the second highest in the world[3]. Meanwhile, with the improvement of neonatal diagnosis and care, the application of prenatal steroid hormones and postnatal pulmonary surface-active substances, mechanical ventilation, nutritional support, and other interventions, the survival rate of preterm infants, especially very low birth weight infants (VLBWI) and extremely low birth weight infant (ELBWI), has improved significantly; along with the increase in the survival rate, the incidence of BPD has

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also increased year by year[4]. In the United States, there are 10,000-15,000 new cases of BPD every year, and the incidence of BPD in preterm infants born at ≤ 28 weeks of gestational age is about 40.8%, and the incidence in preterm infants born at < 24 weeks of gestational age can be as high as 67.4%[5]. A multicenter retrospective study[6] in China showed that the incidence of BPD was 11.4% in preterm infants born at 28-31 + 6 weeks of gestational age and 37.9% in preterm infants born at 26-27 + 6 weeks of gestational age. The prevention and treatment of BPD have become one of the most important problems for doctors in the neonatal intensive care unit (NICU).

Any newborn with oxygen-dependent (oxygen concentration > 21%) ≥ 28 days is defined as BPD, which usually occurs in preterm infants. Previously, classic BPD is induced by severe Neonatal respiratory distress syndrome (NRDS). The pathogenesis basis of classic BPD is oxygen toxicity and mechanical ventilation-related volume/pressure trauma. It is characterized pathologically by chronic inflammation and fibrosis of the lung parenchyma, airway smooth muscle proliferation, and squamous epithelial cell metaplasia[7,8]. The incidence of classic BPD has decreased significantly in recent years due to the implementation of various protective lung ventilation strategies[9]. When preterm infants have oxygen dependence even if they do not receive hyperoxia and mechanical ventilation after birth and have decreased number of alveoli, increased size of alveoli, simplified alveolar structure, and mild alveolar and airway damage and fibrosis, it is called new BPD[9,10]. The pathology of new BPD is characterized by blocked alveolar development, impaired septal formation, and pulmonary microvascular dysplasia. Foreign studies[10] have suggested that children with BPD are not only at risk for pathological airway changes but also for cardiovascular sequelae, and pulmonary hypertension (PH) is the most common complication. According to some studies[11] on BPD combined with PH, about 18% of preterm infants with a birth mass < 1,500 g have varying degrees of PH during hospitalization, and the incidence of PH in children diagnosed with BPD is as high as 25-40%. Zhang and Wang[12] analyzed the clinical data and outcomes of 102 ultra-premature infants born at gestational age < 28 weeks and found that PH was a high-risk factor for the development of BPD in ultra-premature infants.

The right heart float catheterization is the gold standard for assessing PH, but it is difficult to apply in neonates because of its invasive nature. American Heart Association (AHA) and the American Thoracic Society (ATS) (AHA/ATS) 2015 guidelines state that echocardiographic indexes are recommended to screen for PH in children diagnosed with BPD and tricuspid regurgitation (TR) is the most commonly used to assess PH[13]. When TR exists, the right ventricular pressure gradient is estimated by peak TR velocity (TRmax) [the pressure difference between the right ventricle and the left atrium = 4 × (TR2max)], and the systolic pulmonary artery pressure (SPAP) is the right atrial pressure [10 mmHg (1.33 kPa)] plus the estimated right ventricular pressure gradient. One study[14] confirmed that there was no significant difference between the echocardiographic estimate of SPAP and the right heart catheter measured value. This study investigates the role of echocardiographic parameters in diagnosing bronchopulmonary dysplasia (BPD) in preterm infants. The correlation between TR velocity (m/s) and the occurrence of BPD was also investigated by analyzing the differences in various echocardiographic parameters between the BPD and non-BPD groups of preterm infants. This work provides an objective clinical indicator to assess the occurrence of BPD in preterm infants and is helpful to diagnose and intervene BPD timely.

Patients and Methods

Ethical Declaration

The present study procedures were conducted in compliance with the latest version of the Declaration of Helsinki issued by the World Medical Association, and all protocols of this study were approved by Institutional Review Board/Ethics Committee (NICU/2019/019) of The First People's Hospital of Yinchuan, Ningxia Medical University, Yinchuan, China, and informed consent was obtained from the parents or guardians of the children.

General Data

Ninety preterm infants hospitalized in the NICU of our hospital between January 2020 and January 2021 were selected as the study subjects. They were divided into the BPD group (observation group) and the non-BPD group (control group) according to whether they were accompanied by BPD or not. There were 54 study subjects in the control group and 36 study subjects in the observation group, and the clinical case information of both groups is shown in Table I.

Table I. Comparison of general data of two groups of subjects [$\bar{x} \pm s$, cases (%)].

Group		Control group (n = 36)	Observation group (n = 54)	t/χ^2	*p*
Gestational age (weeks)		30.09 ± 2.28	27.88 ± 1.85	4.266	< 0.001
Gender	Male	17 (47.22)	25 (46.29)	0.011	0.915
	Female	19 (52.78)	29 (53.71)		
Birth weight (kg)		1.31 ± 0.18	1.19 ± 0.20	2.546	0.013
Mode of delivery	Spontaneous labour	15 (41.67)	23 (42.59)	0.004	0.951
	caesarean birth	21 (58.33)	31 (57.41)		
Basic diseases	Neonatal respiratory distress syndrome	21 (58.33)	42 (77.78)	2.564	0.109
	Neonatal pneumonia	23 (63.89)	52 (96.30)	10.422	0.001
	Neonatal sepsis	25 (69.444)	43 (79.63)	0.884	0.347
	Patent ductus arteriosus	20 (55.56)	33 (61.11)	0.195	0.659
	Neonatal necrotizing enterocolitis	2 (5. 56)	5 (9.26)	0.329	0.566
Complication	Neonatal asphyxia	14 (25.93)	21 (58.33)	8.058	0.005
	Pulmonary hemorrhage	2 (5.56)	5 (9.26)	1.274	0.259
	Intraventricular hemorrhage	7 (19.44)	3 (5.56)	1.883	0.170
	Purulent meningitis	3 (5.56)	5 (9.26)	0.329	0.566
	anemia	27 (75.00)	41 (75.93)	0.045	0.831
	Retinopathy of prematurity	9 (25.00)	24 (44.44)	3.389	0.066
	Pulmonary hypertension	1 (2.78)	8 (14.81)	2.266	0.132
Premature rupture of membranes greater than 18 hours		4 (11.11)	9 (16.67)	0.259	0.611
Oxygen inhalation time (days)		23.65 ± 9.68	37.62 ± 11.45	5.327	< 0.001

All subjects selected for this study followed the inclusive and exclusive criteria. The inclusive criteria included gestational week < 32 weeks, weight < 1.5 kg, admission to the NICU within 1 hour after birth, complete and clear clinical data, and length of stay < 28 days. The subjects in the observation group met the diagnostic criteria of BPD[15]. The family members of all the subjects have signed the informed consent for the research project. The exclusive criteria included having complex congenital heart disease, chromosomal abnormalities, inherited metabolic diseases, or severe congenital malformations.

The sample size was calculated using the following formula:

$$n = 2\,(Za+Z1-\beta)^{2\sigma 2} / \Delta^2$$

Where n is the required sample size; while in Zα, Z is a constant (set by convention according to the accepted α error and whether it is a one-sided or two-sided effect). In the above-mentioned formula, σ is the standard deviation (estimated) and Δ the difference in the effect of two interventions which is required (estimated effect size). The power was set to 90%.

Examination Method

The infant was examined by Doppler cardiac ultrasonography using a Philips IE Elite3 color Doppler cardiac ultrasound diagnostic instrument with S8-3 probe and a probe frequency of 3-8 MHz on the 14^{th} day after admission. The infant took a supine position and was probed *via* thoracic approach. The parasternal left ventricular long-axis section, aortic root short-axis section, apical four-chamber and five-chamber sections, subcostal two-chamber and four-chamber sections, and suprasternal fossa aortic arch section were probed one by one. The two-dimensional echocardiography was used to observe the heart and the positional relationship and dimension ratio, measure the size of cardiac chambers and the dimension, wall thickness, and motion range of the aorta, and measure cardiac function. The thickness and motion range of the valve and the existence of continuous atrioventricular septal interruption were observed. The blood flow direction and property, the existence of backflow at the valve orifice, and the existence of shunt between the atrioventricular septum and aorta were observed by color Doppler. The blood flow velocity at different valve orifices was measured by pulse Doppler, and the shunt velocity was measured by color Doppler. The standard section images and abnormal site section images or dynamic video data were stored in the ultrasound imaging workstation. The above examinations were done by two or three people in the same cardiac ultrasound team of our hospital to ensure scientific and accurate examination results.

Diagnostic Criteria of PH

The most accurate way to assess pulmonary arterial pressure (PAP) is to detect TR by Doppler cardiac ultrasound. The peak velocity of TR is directly related to the right ventricular pressure, and the right ventricular systolic pressure (RVSP) is essentially equivalent to SPAP. The relationship between the velocity of TR and the right ventricular and atrial pressure difference can be calculated using a fluid mechanics formula: RVSP = right atrial pressure (usually assumed to be 5 mmHg) + (4 × $TRVmax^2$)[16]. Under Doppler heart color ultrasound, PH is diagnosed when SPAp > 35 mmHg or > 2/3 systemic circulation systolic blood pressure or there is a right-to-left shunt at the arterial duct level or the atrial level[17].

Observation Indexes

Left atrium dimension (LAD), left ventricular end-diastolic dimension (LCDd), left ventricular end-systolic dimension (LVSd), left ventricular posterior wall dimension (LVPWd), right ventricle dimension (RVD), aortic root dimension (ARD), and ventricular wall motion range. The left ventricular ejection fraction (LVEF) and left ventricular shorting fraction (LVFS) were calculated based on LVDd and left ventricular end-systolic diameter (LVSd). The arterial duct situation: it was observed whether there was a shunt; if there was, the shunt site, direction, velocity, and pressure difference were measured. The situation of atrioventricular septum: it was observed whether there was a continuous interruption; if there was, the defect size, shunt direction, and shunt volume were measured. The situation of TR: it was observed whether there was a regurgitation; if there was, the regurgitation velocity and pressure difference were measured.

Statistical Analysis

Statistic Package for Social Science (SPSS) 23.0 (IBM Corp., Armonk, NY, USA), was used. The measurement data were expressed by Mean±standard deviation (x±s) and processed by t-test. The count data were expressed by frequency number or percentage and treated by χ^2 test. The predictive efficiency of the index was evaluated using the receiver operator characteristic (ROC) curve. The correlation between TR velocity and BPD was analyzed by Spearman rank correlation. The difference was considered statistically significant if $p < 0.05$.

Results

Comparison of Cardiac Ultrasound Results Between Two Groups of Preterm Infants

The incidence of patent ductus arteriosus (PDA) and PH were higher in the observation group than in the control group, and the levels of LVEF and LVFS were lower than in the control group; the differences were statistically significant ($p < 0.05$). The differences in the incidence of patent foramen ovale (PFO), atrial septal defect (ASD), and ventricular septal defect (VSD) between the two groups were not statistically significant ($p > 0.05$) (Table II).

Comparison of TR Between Two Groups of Premature Infants

Thirty-eight cases (70.4%) in the observation group and 16 cases (44.4%) in the control group

Table II. Comparison of ultrasound results between two groups

Group	PH (n, %)	PDA (n, %)	PFO (n, %)	VSD (n, %)	ASD (n, %)	LVEF (%, x±s)	LVFS (%, x±s)
Observation group (n = 54)	21 (38.9)	35 (64.8)	19 (35.2)	0	37 (68.5)	51.15 ± 6.83	28.82 ± 5.28
Control group (n = 36)	1 (2.8)	5 (13.9)	12 (33.3)	0	24 (66.7)	67.73 ± 6.91	34.96 ± 3.57
χ^2/t	6.791	7.246	0.026	/	0.006	9.568	10.789
p	> 0.001	< 0.001	0.872	/	0.928	< 0.001	< 0.001

PDA: patent ductus arteriosus; PH: pulmonary arterial hypertension; PFO: patent foramen ovale, ASD: atrial septal defect; VSD: ventricular septal defect; LVEF: left ventricular ejection fraction; LVFS: left ventricular fractional shortening. x±s (Mean±Standard deviation).

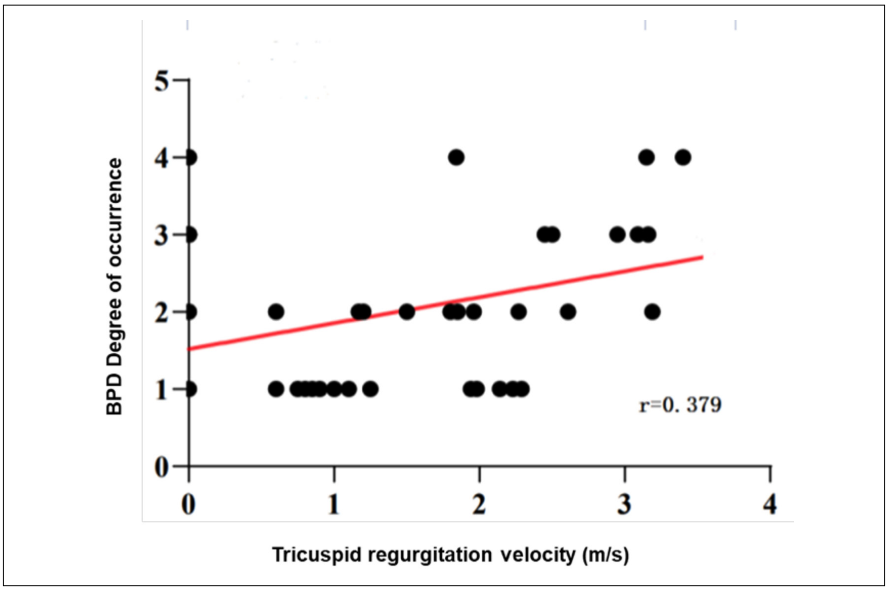

Figure 1. The relationship between TR velocity and severity of BPD. 1 refers to non-BPD, 2 refers to mild BPD, 3 refers to moderate BPD, and 4 refers to severe BPD.

had TR. The proportion of TR premature infants was significantly higher in the observation group than in the control group $\chi^2 = 5.137$ $p < 0.05$). The examination results of TR velocity (m/s) in the two groups of preterm infants were compared. The results showed that the TR velocity in the observation group was 2.37 ± 0.76 (m/s), which was significantly higher than that in the control group (1.31 ± 0.54) ($t = 4.971$, $p < 0.05$). The higher the TR velocity, the higher the incidence and severity of BPD. Spearman correlation analysis showed a positive correlation between TR velocity (m/s) and BPD ($r = 0.379$, $p < 0.05$), as shown in Figure 1.

Prediction of Occurrence of BPD with TR Velocity

A ROC curve was drawn by taking TR velocity (m/s) as the variable and the control group as the reference level to assess the prediction efficiency of TR velocity for the occurrence of BPD. The area under the curve (AUC) was 0.735 (95% CI: 0.624-0.849, $p < 0.05$). When the critical value was 1.45 m/s, the sensitivity was 88.0%, and the specificity was 62.6%, as shown in Figure 2.

Discussion

In our study, the observation group had a significantly higher incidence of PDA and PH than the control group, while the levels of LVEF and LVFS were significantly lower than in the control group. There were no significant differences in the incidence of PFO, ASD, and (VSD between the two groups. The proportion of premature infants with tricuspid regurgitation (TR) was significantly higher in the observation group than in the control group. The TR velocity in the observation group was significantly higher than that in the control group, and there was a positive correlation between TR velocity and BPD severity. The area under the curve (AUC) of the ROC curve drawn to assess the prediction efficiency of TR velocity for the occurrence of BPD was 0.735, indicating that TR velocity has moderate predictive power for the occurrence of BPD.

BPD is one of the most common and serious respiratory disorders in preterm infants, especially in very low birth weight and ultra-low birth weight infants. In recent years, the clinical presentation of BPD has changed, and the incidence of new BPD has increased, affecting the long-term prognosis of preterm infants and even leading to death. Prediction of BPD will allow clinicians and researchers to identify high-risk infants who are more likely to benefit from early targeted treatment1. Therefore, clinical emphasis should be placed on finding early diagnostic methods for predicting BPD in

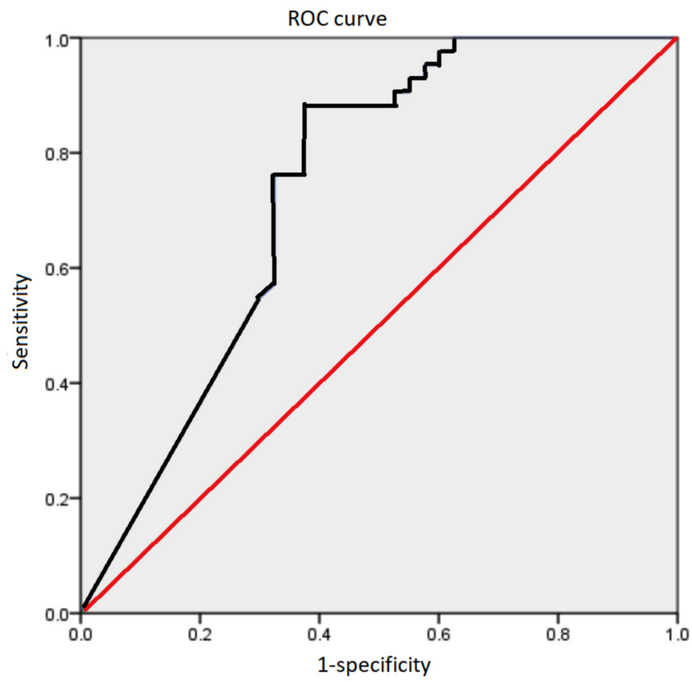

Figure 2. The ROC curve of predicting BPD occurrence with TR velocity.

preterm infants to identify children at risk of BPD after birth. Previous studies[19,20] have focused on biochemical markers, which do not have ideal diagnostic accuracy, and most of them remain indicators that are not available in daily practice. In recent years, echocardiography has been widely used in the diagnosis of neonatal lung diseases and has shown its unique advantages. Alvarez-Fuente et al[21] evaluated the diagnostic efficacy of clinical symptoms, echocardiography, and biomolecular markers in 47 preterm infants under 29 weeks with BPD. The results showed that the diagnostic efficacy of the echocardiograph was superior to the other indicators, and its sensitivity and specificity for predicting moderate or severe BPD were 61.5% and 85%, respectively. This study applied echocardiography to two groups of preterm infants to analyze the predictive effect of the echocardiography-related parameters on BDP in detail. The results showed that the incidence of PDA was higher in the observation group than in the control group, which was similar to the findings of Liu et al[22], which highlights the importance of early detection and prevention of these risk factors to reduce the incidence of BPD in premature infants. PDA leads to cardiac blood shunting to induce pulmonary stasis, reduced pulmonary compliance, and prolonged mechanical ventilation, increasing the risk of BPD[23]. Schena et al[24] retrospectively analyzed the clinical data of 242 preterm infants with gestational age ≤ 28 weeks to explore the correlation between the duration of PDA and the development of BPD and found that each week of a hemodynamically PDA increased the risk of BPD by 70%. Preterm infants with PDA have increased pulmonary blood flow, and excessively large pulmonary blood flow inhibits pulmonary vascular development, which is a characteristic pathology of BPD.

In addition, in this study, LVEF and LVFS levels were lower in the observation group than in the control group, suggesting the existence of different degrees of hemodynamic changes and changes in cardiac function during BPD in preterm infants, i.e., reduced cardiac blood output and myocardial contractility. With the exacerbation of BPD, abnormal hemodynamic indexes increased, and severe changes in cardiac function were observed. During BPD, PAP increases, and right ventricular load increases, causing decreases in pulmonary valve flow acceleration time and ejection time;

moreover, redistribution of blood flow caused by hypoxia increased pulmonary vascular resistance[25,26].

The results of this study showed that 21 cases (38.9%) in the observation group had PH, which was consistent with that mentioned in Slaughter's report[2]. The incidence of PH in preterm infants in the observation group was significantly higher than that in the control group. A retrospective analysis of data from 311 preterm infants by Wei et al[28] showed that the incidence of PH in preterm infants in the BPD group was significantly higher than that in the non-BPD group, which is consistent with the results of this study. In addition, the incidence of TR and the TR velocity in the observation group were higher than those in the control group in this study, and a positive correlation was found between the TR velocity and the occurrence of BPD, which is rarely reported in the literature. The reason was analyzed. The increased PAP increased the pressure load on the right ventricle, resulting in TR, but most preterm infants' PAP did not meet the diagnostic criteria for PH, so it was manifested as TR only. The increased PAP can increase pulmonary circulatory resistance and lead to abnormal pulmonary capillary development[29]. In addition, elevated PAP disrupts pulmonary vascular endothelial cells and accelerates pulmonary vascular remodeling, ultimately leading to BPD-like pulmonary vascular changes. In a previous study[30], a cohort study was conducted on 161 preterm infants, 112 in the pulmonary infection group and 49 in the non-pulmonary infection group. The PAP was calculated according to the TR pressure difference. It was found that the PAP of preterm infants in the pulmonary infection group was significantly higher than that in the non-pulmonary infection group, and PAP was positively correlated with the infection severity. During pulmonary infection, inflammatory cell infiltration leads to reduced alveolar diffusion area and prolonged diffusion time, which induces swelling of lung endothelial cells or constriction of lung capillaries. Higher PAP increased the right ventricular ejection resistance. The higher the PAP, the higher the TR velocity, and the higher the risk of BPD. The only limitation of this study was that it retrospectively analyzed the clinical data of preterm infants with BPD admitted to the NICU of our hospital in the past year, which was a single-center clinical study with a limited sample size. Multi-center, large-sample retrospective and prospective studies of clinical data are needed.

Conclusions

The study investigated the role of echocardiographic parameters, particularly the TR velocity, in diagnosing BPD in preterm infants. The study found that preterm infants with BPD had a significantly higher incidence of PDA and PH, as well as lower levels of LVEF and LVFS, compared to preterm infants without BPD. The study suggests that echocardiography can be useful for early detection of PH and impaired cardiac function in preterm infants, which may help reduce the mortality rate. The study also highlights the potential value of TR velocity as a diagnostic marker for BPD in preterm infants. It is worth noting that further research is needed to validate these findings and explore the potential clinical applications of echocardiographic parameters in the early diagnosis of BPD in preterm infants.

Ethics Approval

This study was approved by Institutional Review Board/Ethics Committee (NICU/2019/019) of The First People's Hospital of Yinchuan, Ningxia Medical University, Yinchuan, China.

Informed Consent

Informed consent was obtained from each and every participant's guardian.

Data Availability

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declared that they have no conflicts of interest regarding this work.

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Authors' Contributions

LM, LWU, JW: Designed and performed the planned review, analyzed the review data, and prepared the paper. YWU, XS, SL: Participated in collecting the materials related to the review. LM and JW: Corresponding authors designed the experiments and revised the manuscript.

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References

1) Rossor T, Greenough A. Advances in paediatric pulmonary vascular disease associated with bronchopulmonary dysplasia. Expert Rev Respir Med 2015; 9: 35-43.
2) Baker CD, Abman SH, Mourani PM. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Pediatr Allergy Immunol Pulmonol 2014; 27: 8-16.
3) Cheong JLY, Doyle LW. An update on pulmonary and neuro-developmental outcomes of bronchopulmonary dysplasia. Semin Perinatol 2018; 42: 478-484.
4) Zhu XP. Changes in the definition of bronchopulmonary dysplasia and related researches progress. Chinese J Child Health Care 2019; 27: 1047-1049.
5) Nakagawa Y, Nishikimi T, Kuwahara K. Atrial and brain natriuretic peptides: Hormones secreted from the heart. Peptides 2019; 111: 18-25.
6) Jiang S, Yan W, Li S, Zhang L, Zhang Y, Shah PS, Shah V, Lee SK, Yang Y, Cao Y. Mortality and morbidity in infants < 34 weeks' gestation in 25 NICUs in China: a prospective cohort study. Front Pediatr 2020; 8: 33.
7) Mowitz ME, Ayyagari R, Gao W, Zhao J, Mangili A, Sarda SP. Health Care Burden of Bronchopulmonary Dysplasia Among Extremely Preterm Infants. Front Pediatr 2019; 7: 510.
8) Zuo JY, Wang YR, Yang YT. Advances in the pathogenesis of bronchopulmonary dysplasia in preterm infants. Int J Pediatr 2019; 46: 831-834.
9) Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, Ryan RM, Kallapur SG, Steinhorn RH, Konduri GG, Davis SD. Bronchopulmonary dysplasia: executive summary of a workshop. J Pediatr 2018; 197: 300-308.
10) Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr 2011 23: 167-172.
11) Nagiub M, Kanaan U, Simon D, Guglani L. Risk factors for development of pulmonary hypertension in infants with bronchopulmonary dysplasia: systematic review and meta-analysis. Paediatr Respir Rev 2017 23: 27-32.
12) Zhang S, Wang HQ. Analysis of factors influencing bronchopulmonary dysplasia in extremely preterm infants. Chinese J Child Health Care 2019 27: 1059-1061.
13) Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation 2015 132: 2037-2099.
14) Hansmann G, Apitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102: 67-85.
15) Shao XM, Ye HM, Qiu XS. Practical Neonatology [M]. 5th Ed. Beijing: People's Medical Publishing House 2019; 727-732.
16) Wang CH, Shi LP, Ma XL, Du LZ. Clinical features and prognosis of bronchopulmonary dysplasia complicated by pulmonary hypertension in preterm infants. Chinese J Contem Pediatr 2018; 20: 893-896.
17) del Cerro MJ, Sabaté Rotés A, Carton A, Deiros L, Bret M, Cordeiro M, Verdu C, Barrios MI, Albajara L, Gutierrez-Larraya F. Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes. Pediatr Pulmonol 2014; 49: 49-59.
18) Tian XY, Zhang XD, Li QL, Shen Y, Zheng J. Biological markers in cord blood for prediction of bronchopulmonary dysplasia in premature infants. Clin Exp Obstet Gynecol 2014; 41: 313-318.
19) Förster K, Sass S, Ehrhardt H, Mous DS, Rottier RJ, Oak P, Schulze A, Flemmer AW, Gronbach J, Hübener C, Desai T. Early identification of bronchopulmonary dysplasia using novel biomarkers by proteomic screening. Am J Respir Crit Care Med 2018; 197: 1076-1080.
20) Rivera L, Siddaiah R, Oji-Mmuo C, Silveyra GR, Silveyra P.Biomarkers for bronchopulmonary dysplasia in the preterm infant. Front Pediatr 2016; 4: 33.
21) Alvarez-Fuente M, Moreno L, Lopez-Ortego P, Arruza L, Avila-Alvarez A, Muro M, Gutierrez E, Zozaya C, Sanchez-Helguera G, Elorza D, Martinez-Ramas A. Exploringclinical, echocardiographic and molecular biomarkers to predict bronchopulmonary dysplasia. PLoS One 2019; 14: e0213210
22) Willis K A, Weems M F. Hemodynamically significant patent ductus arteriosus and the development of bronchopulmonary dysplasia. Congenit Heart Dis 2019; 14: 27-32.
23) Liu GR, Ma JX, Mao J, Li J. Influencing factors for bronchopulmonary dysplasia in VLBWI and ELBWI. Inter J Pediatr 2018; 45: 794-798.

24) Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, Fumagalli M. Association between Hemodynamically Significant Patent Ductus Arteriosus and Bronchopulmonary Dysplasia. J Pediatr 2015; 166: 1488-1492.
25) Zuo JY, Wang YR, Yang YT. Research Progress on the pathogenesis of bronchopulmonary dysplasia in premature infants. Inter J Pediatr 2019; 46: 4.
26) Llili. Pathogenesis and treatment of bronchopulmonary dysplasia in premature infants. Inter J Pediatr 2018; 45: 4.
27) Slaughter JL, Pakrashi T, Jones DE, South AP, Shah TA. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol 2011; 31: 635-640.
28) Wei JQ, Zhang ZM, Zhang XY, Liu J, Feng ZC. An analysis of risk factors of premature infants with bronchopulmonary dysplasia. Chinese J Woman Child Health Res 2010; 21: 261-263.
29) Valenzuela D, Moya F, Luco M, Tapia JL. [The role of pulmonary hypertension on bronchopulmonary dysplasia]. Rev Chil Pediatr, 2017; 88: 699-706.
30) Li HQ, Jiang FX, Zhong XY, Zhang Y. Echocardiographic study of pulmonary artery pressure in neonates with pulmonary infection. Chinese J Nosocomiol 2019; 29: 1717-1721.