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Predictive Tool for Closure of Ductus Arteriosus with Pharmacologic or Surgical Treatment in Preterm Infants

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Abstract

To construct a model with the indices obtained by echocardiography to predict whether patent ductus arteriosus (PDA) was required to be treated with pharmacologic treatment or surgical ligation, we performed a prospective observational study, including all neonates with gestational age ≤ 30 weeks and assessed the hemodynamics of PDA by serial daily echocardiography examination at postnatal age of 0–12 h, 24 h, 48 h, and 72 h, respectively. The infants were classified in two groups based on whether they were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and/or surgical ligation to close the PDA from the second week after birth. We compared the echocardiographic indices between the two groups and utilized the indices to construct a model to predict which premature infants' PDA requires intervention. The results showed that a total of forty-two preterm infants were enrolled in the study. 15 (35.7%) preterms were in the intervention group and 27 (64.3%) preterms were in the non-intervention group. Compared with the non-intervention group, the intervention group had a higher proportion of left ventricular volume overload and systemic shunt effect. In addition, the combined indicators of PDA size/weight > 3.2 mm/kg and LA/Ao > 1.4 at postnatal age of 72 h had a highest value to predict whether PDA requires intervention. These findings denoted that serial daily echocardiographic assessment can be useful in predicting whether a PDA will be closed with NSAIDs and/or surgical ligation in preterm infants with gestational age ≤ 30 weeks.

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Keywords Echocardiographic assessment · Hemodynamically significant patent ductus arteriosus · Newborn · Patent ductus arteriosus · Preterm infants

Abbreviations

AKI	Acute kidney injury
ASD	Atrial septal defect
BPD	Bronchopulmonary dysplasia
COX	Inhibitors cyclooxygenase inhibitors
DA	Ductus arteriosus
DAo	Descending aorta
E:A	The ratio of mitral valve E:A
EF	Ejection fraction
E:E'	The ratio of mitral valve E:E'
EUGR	Extrauterine growth retardation
FS	Fractional shortening
hs-PDA	Hemodynamically significant patent ductus arteriosus
IVH	Intraventricular hemorrhage
LVO	Left ventricular output
LA/Ao	Ratio of left atrial to aortic root diameter
LVEDd	Left ventricular end-diastolic diameter
LPA	Left pulmonary artery
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PNAC	Parenteral nutrition-associated cholestasis
POLUS	Point-of-care ultrasound
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
VSD	Ventricular septal defects

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Introduction

Patent ductus arteriosus (PDA) is a major cause of cardiovascular compromise during transition from fetal to neonatal circulation in premature infants [1]. PDA is usually

accompanied by significant left-to-right shunt through the ductus arteriosus (DA) and can be confirmed by echocardiography. Clinical manifestations include systemic hypoperfusion and pulmonary hyperperfusion [2]. Furthermore, severe morbidities, such as acute kidney injury (AKI), pulmonary hemorrhage, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and increased mortality, are associated with PDA [3–7]. Conventionally, treatment options for PDA include the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and/or surgical ligation if conservative treatment fails in premature infants. However, there are few consensus on the management of PDA, including whether, when, and how to treat, and few clinical studies on early serial daily echocardiographic assessment of the hemodynamics of PDA to predict whether pharmacologic or surgical treatment are required in the very preterm infants. Therefore, we performed this study to assess the characteristics of DA, indices of pulmonary overcirculation, and systemic shunt effect continuously and dynamically and constructed a model with echocardiographic indices to predict the probability of PDA that ultimately requires intervention.

Methods

With the approval of the Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine (IRB No. 2018-IRB-073), a prospective observational study was conducted to investigate the clinical data and echocardiographic indices of 42 preterm infants born at gestational age (GA) ≤ 30 weeks who were admitted to the neonatal intensive care unit of the Children's Hospital, Zhejiang University School of Medicine from October 2018 to December 2020. Written informed consent was obtained from guardian participants. The exclusion criteria for this study were as follows: (1) the age at admission was > 12 h after birth; (2) infants who died or gave up treatment within 72 h of life; (3) infants complicated with complex congenital heart disease except for a small patent foramen ovale (PFO)/atrial septal defect (ASD)/ventricular septal defect (VSD); (4) the parents refused. In this study, we divided the patients into intervention group and non-intervention group according to whether PDA was treated or not during hospitalization: (1) intervention group: closure with oral non-steroidal anti-inflammatory drugs (NSAIDs) and/or surgical ligation; (2) non-intervention group: spontaneous closure without pharmacologic or surgical treatment.

The indications for treatment were based on whether PDA was symptomatic including respiratory compromise (e.g., requiring persistent mechanical support), cardiac insufficiency, or large left-to-right ductus shunt with evidence of hemodynamic compromise, such as reversal of flow in the descending aorta during diastole, feeding intolerance, oliguria, hypotension, or wide pulse pressure in the study. Pharmacologic treatment was considered if conservative measures have failed to control the above symptoms from the second week after birth. PDA surgical ligation was generally performed in the patients which NSAIDs treatment was unsuccessful after the end of the two course or contraindicated.

Transthoracic echocardiography was performed using GE Vivid™ iq bedside ultra-portable Doppler diagnostic ultrasound system with a 12S-RS transducer (GE Healthcare). We routinely assessed cardiac function (EF, FS, E:A, and E:E'), PDA characteristics (patency, dimension), indices of left heart volume ((LA:Ao, left ventricular end-diastolic diameter (LVEDd), end-diastolic velocity of the left pulmonary artery (LPA), left ventricular output (LVO)) and pressure (mitral valve E:A) loading, and the presence of retrograde diastolic blood flow in a post-ductal artery (descending aorta, DAo) in participants at postnatal age of 0–12 h, 24 h, 48 h, and 72 h, respectively. The serial daily echocardiographic assessments were performed by the same neonatologist who had received the training of critical ultrasound course. The data of patients' demographics and clinical outcomes were recorded.

Statistical Analysis

Statistical analysis was performed using the SPSS version 21.0 and GraphPad Prism 7.00. We compared the echocardiographic data of the intervention group and the non-intervention group. Statistical analysis was performed using t test and Mann–Whitney u tests for continuous variables according to whether variables obey normal distribution or not. X^2 or Fisher exact tests were used for categorical variables as appropriate. Data were expressed as median with quartile range (M (Q1, Q3)) for continuous variables or as a percentage of patients in a given categorical variable. All probability (p) values were two-tailed and a value less than 0.05 was considered statistically significant.

Univariate and multivariate regression analyses were used to analyze the data variables of echocardiography to determine predictors of PDA requiring NSAIDs intervention and/or surgical ligation. Multivariable logistic regression analysis was performed to analyze the variables at postnatal age of 0–12 h, 24 h, 48 h, and 72 h, respectively, which using stepwise logistic regression with forward selection and backward elimination by removing variables that had a p value of greater than 0.05. Results were expressed as OR with 95%CI. The predictive power of multivariable model was evaluated by the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Based on the results of the multivariable regression analysis, which the

largest AUC was chosen. Cut-off values of the results were chosen on the basis of the ROC curve of each variable and outcome, which located in the maximum value of Youden Index according to the sensitivity and specificity.

Results

A total of forty-two very preterm infants met the inclusion criteria and were enrolled during the study period (Fig. 1). These were categorized into two groups: 15 (35.7%) in the intervention group: gestational age (GA) was 27.2 ± 1.1 weeks and birth weight ranged from 750 to 960 g (median 880 g) and 27 (64.3%) in the non-intervention group: GA was 28.8 ± 1.5 weeks and birth weight ranged from 950 to 1340 g (median 1050 g). Compared with the non-intervention group, the intervention group had a higher proportion of alveolar surfactant use ($p = 0.008$), reintubation within 48 h from extubation ($p = 0.047$), duration of mechanical ventilation ($p < 0.001$), inhale oxygen days ($p = 0.005$), inotropes/vasopressors use ($p < 0.001$), extrauterine growth retardation (EUGR) ($p = 0.029$), IVH grade ≥ 3 ($p = 0.016$), and retinopathy of prematurity (ROP) ($p = 0.004$). The mortality and other clinical manifestations were not statistically significant between the two groups (Table 1).

The diameter of the DA in preterm infants of the intervention group increased gradually within 72 h after birth, while the trend in the non-intervention group was completely opposite. Compared with the non-intervention group, the diameters of DA at postnatal age of 0–12 h, 24 h, 48 h, and 72 h in the intervention group were larger, with significant statistical difference ($p = 0.028$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In addition, two groups had statistically significant difference compared with echocardiographic indices of pulmonary overcirculation, including LVO at postnatal age of 24 h, 48 h, and 72 h ($p = 0.001$, $p = 0.007$, and $p = 0.002$, respectively), LA/Ao at postnatal age of 72 h ($p < 0.001$), and end-diastolic flow of the LPA at 24 h, 48 h, and 72 h ($p = 0.026$, $p < 0.001$, and $p < 0.001$, respectively). The presence of retrograde diastolic blood flow of the DAo represents an index of systemic shunt effect. The incidence of diastolic reverse flow of the DAo was 26.7%, 80%, and 86.7% at postnatal age of 24 h, 48 h, and 72 h, respectively, in the intervention group, which were significantly higher than those of the non-intervention group (0.0%, 14.8%, and 18.5%, $p = 0.012$, $p < 0.001$, and $p < 0.001$, respectively). The other parameters of left ventricular systolic and diastolic function except for mitral valve E/E′ at the postnatal age of 72 h ($p = 0.014$) were not statistically significant between the two groups (Table 2).

Risk Factors for PDA that Need Pharmacologic and/or Surgical Ligation Intervention Analyzed by Logistic Regression Analysis

There were fourteen statistically significant variables (one variable at postnatal age of 0–12 h, three variables at

Fig. 1 Flowchart of enrolled participants
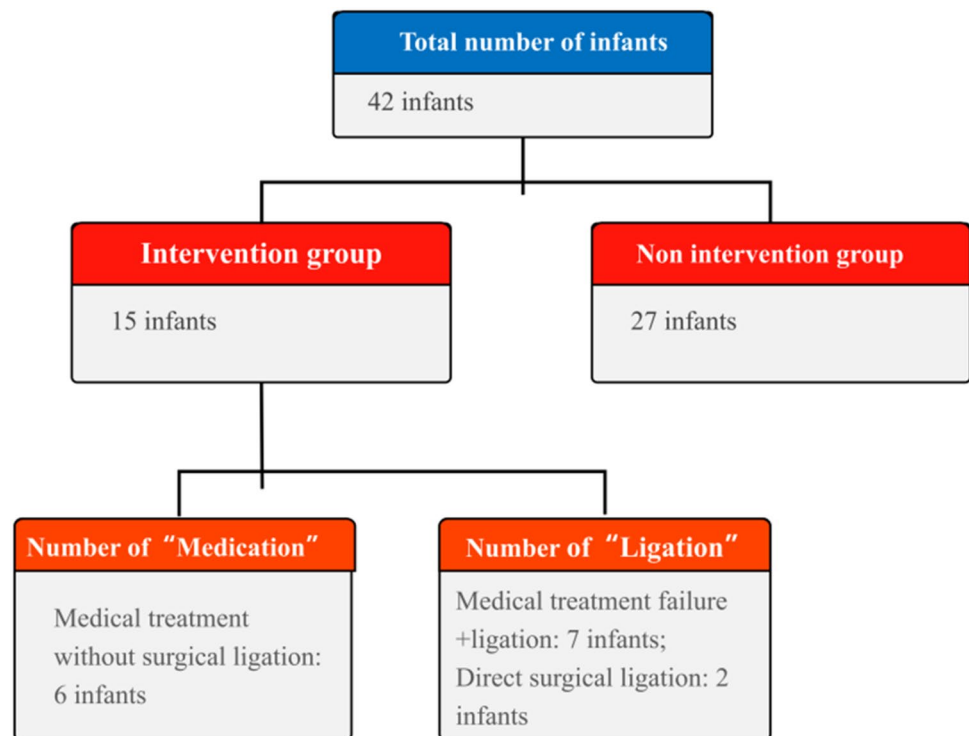
Table 1 Comparison of the demographic and clinical characteristics of the study cohort

	Intervention group ($n=15$)	Non-intervention group ($n=27$)	p Value
Clinical Characters			
Male gender	10(66.7%)	17(63%)	0.81
Gestational age, weeks*	27.2 ± 1.1	28.8 ± 1.5	0.001
Birth weight, g*	880(750–960)	1050(950–1340)	0.001
Use of surfactant*	13(86.7%)	12(44.4%)	0.008
Reintubation within 48 h from extubation *	4(26.7%)	1(3.7%)	0.047
Duration of mechanical ventilation*	25.7 ± 20.5	3.6 ± 6.1	< 0.001
Non-invasive ventilation	30.7 ± 18.9	20 ± 17.1	0.068
Inhale oxygen days*	70.5 ± 36.6	38.1 ± 32.4	0.005
BPD	14(93.3%)	17(63%)	0.075
VAP/Lower respiratory infection	8(53.3%)	9(33.3%)	0.206
Late onset sepsis	8(53.3%)	9(3.3%)	0.206
Use of inotropes/vasopressors*	10(66.7%)	2(7.4%)	< 0.001
Feeding intolerance	14(93.3%)	17(63%)	0.075
Total enteral feeding	45(39–70)	38(20–65)	0.27
PNAC	5(33.3%)	7(25.9%)	0.879
EUGR*	9(60%)	7(25.9%)	0.029
ROP*	10(66.7%)	6(22.2%)	0.004
Length of hospital stay	88(62–100)	60(44–77)	0.059
Complications and mortality			
NEC any stage	2(13.3%)	5(18.5%)	1.000
Pulmonary hemorrhage	5(33.3%)	2(7.4%)	0.077
IVH grade ≥ 3*	5(33.3%)	1(3.7%)	0.016
Death	3(20%)	2(7.4%)	0.329

BPD Bronchopulmonary dysplasia, *VAP* Ventilator-associated pneumonia, *PNAC* Parenteral nutrition-associated cholestasis, *EUGR* Extrauterine growth retardation, *ROP* Retinopathy of prematurity, *NEC* Necrotizing enterocolitis, *IVH* Intraventricular hemorrhage

*Indicates parameters found to be statistically significant ($p < 0.05$)

postnatal age of 24 h, four variables at postnatal age of 48 h, and six variables at postnatal age of 72 h) according to univariable logistic regression analysis where PDA requiring NSAIDs intervention and/or surgical ligation was used as the dependent variable, while each continuous variable and categorical variable was used as the independent variable (Tables 3, 4, 5, 6). For the variables that showed no statistically significant difference, but were proven in previous trials, they were still included in the multivariate regression analysis. We, respectively, conducted four times multivariate regression analysis according to the time period of ultrasound screening and the variables included EF, E/E', PDA size/weight, LVO, LA/Ao, LVEDd, end-diastolic flow of the LPA, and retrograde diastolic blood flow of DAo in each regression analysis model. There was only one statistically significant variable in the first three models (PDA size/weight at 0–12 h, LVO at 24 h, PDA size/weight at 48 h) and two statistically significant variables (PDA size/weight at 72 h and LA/Ao at 72 h) in the fourth model, with backward selection were retained in each model (Table 7). The ROC of the four models was drawn with the variables and

outcome, and the area under curve (AUC) was 0.731 (95%CI 0.57–0.89, $p = 0.014$), 0.877 (95%CI 0.75–1, $p < 0.001$), 0.915 (95%CI 0.83–1, $p < 0.001$), and 0.958 (95%CI 0.9–1, $p < 0.001$), respectively (Fig. 2). The largest AUC was seen in the combined indicators of PDA size/weight and LA/Ao at postnatal age of 72 h in the fourth model. Cut-off values of the variables were 3.2 mm/kg and 1.4 for PDA size/weight and LA/Ao, respectively, with sensitivity and specificity of 100% and 88.9%, respectively.

Discussion

Previous studies have demonstrated that PDA is associated with many early and late adverse outcomes [3–7]. In the present study, we identified an inverse relationship between the need for drug treatment and/or ligation in PDA and gestational age and birth weight. The DA left-to-right shunt can result in an interstitial and alveolar pulmonary edema and decreased lung compliance, which leads to higher ventilator settings prolonged ventilation

Table 2 Comparison of the ultrasound parameter of the study cohort

	Intervention group(n = 15)	Non-intervention group (n = 27)	p Value
Variables at postnatal age of 0–12 h			
EF	67.8 ± 6.5	65 ± 8.2	0.263
FS	35(31–37)	33(27–36)	0.193
E/A	0.88 ± 0.19	0.8 ± 0.11	0.157
E/E'	11.5(9.3–17)	9.7(7.8–13.7)	0.253
PDA size/weight(mm/kg)*	2.6 ± 0.7	2.1 ± 0.7	0.028
LVO(ml/kg.min)	190.4(149.1–199.7)	168.1(144.5–186.4)	0.265
LVEDd(mm)	1.1(1–1.3)	1.2(1.1–1.4)	0.105
LA/Ao	1.3(1.2–1.4)	1.4(1.3–1.5)	0.109
LPA(m/s)	0.17(0.1–0.22)	0.13(0.1–0.21)	0.937
DAo	0	0	–
Variables at postnatal age of 24 h			
EF	67.1 ± 10.2	64.9 ± 9.3	0.466
FS	32(28–39)	32(27–38)	0.608
E/A	0.88(0.8–1.1)	0.84(0.78–0.9)	0.168
E/E'	14.8(8.8–16.3)	10.3(9.3–12.3)	0.074
PDA size/weight(mm/kg)*	3.1 ± 0.8	1.8 ± 0.9	< 0.001
LVO(ml/kg.min)*	282.8 ± 71.4	202.9 ± 30.4	0.001
LVEDd(mm)	1.21 ± 0.13	1.26 ± 0.2	0.401
LA/Ao	1.4(1.3–1.6)	1.4(1.3–1.6)	0.631
LPA(m/s)*	0.21(0.15–0.23)	0.12(0.1–0.18)	0.026
DAo*	4(26.7%)	0(0.0%)	0.012
Variables at postnatal age of 48 h			
EF	69.4 ± 4.6	67.7 ± 7.7	0.368
FS	9.7(7.8–13.7)	34.6 ± 5.3	0.591
E/A	0.87(0.78–1.1)	0.87(0.8–0.95)	0.979
E/E'	13.3(7.6–19.3)	9.5(8–12.7)	0.185
PDA size/weight(mm/kg)*	3.4 ± 0.9	1.6 ± 1.1	< 0.001
LVO(ml/kg.min)*	313.2 ± 90.9	234.9 ± 58.2	0.007
LVEDd(mm)	1.27 ± 0.17	1.31 ± 0.22	0.563
LA/Ao	1.5 ± 0.1	1.5 ± 0.2	0.055
LPA(m/s)*	0.24(0.2–0.26)	0.12(0.09–0.2)	< 0.001
DAo*	12(80%)	4(14.8%)	< 0.001
Variables at postnatal age of 72 h			
EF	70.5 ± 7.3	67.1 ± 7.9	0.183
FS	36.7 ± 6.1	34.3 ± 5.9	0.230
E/A	0.92 ± 0.2	0.85 ± 0.11	0.227
E/E'*	16.2 ± 7.3	11.7 ± 4.0	0.014
PDA size/weight(mm/kg)*	3.6(3.2–3.8)	1.5(0–2.1)	< 0.001
LVO(ml/kg.min)*	343.8 ± 89.1	251.3 ± 57.8	0.002
LVEDd(mm)	1.31 ± 0.18	1.3 ± 0.2	0.879
LA/Ao*	1.6(1.5–1.7)	1.3(1.2–1.5)	< 0.001
LPA(m/s)*	0.24(0.22–0.26)	0.12(0.1–0.2)	< 0.001
DAo*	13(86.7%)	5(18.5%)	< 0.001

*Indicates parameters found to be statistically significant ($p < 0.05$)

with the period of oxygen inhalation, and increased risk of pulmonary hemorrhage and BPD [8, 9]. RDS will also aggravate this process as a result of low plasma oncotic pressure and increased capillary permeability, as confirmed by a previous study [10]. Our study shows that the preterm infants in the PDA intervention group required more pulmonary surfactant, longer mechanical ventilation, and oxygen demand. However, there was no significant

Table 3 Results of univariate regression analysis of variables at postnatal age of 0–12 h

Variables	β	SE	Wald	df	p Value	OR	95%CI	
							Lower	Upper
EF	0.050	0.044	1.276	1	0.259	1.051	0.964	1.146
FS	0.049	0.059	0.690	1	0.406	1.050	0.936	1.178
E/A	3.923	2.452	2.559	1	0.11	50.527	0.413	6174.457
E/E'	0.073	0.062	1.372	1	0.242	1.075	0.952	1.214
PDA size /weight (mm/kg)*	1.023	0.496	4.248	1	0.039	2.782	1.052	7.360
LVO(ml/kg.min)	0.010	0.008	1.382	1	0.240	1.010	0.994	1.026
LVEDd(mm)	− 3.216	2.096	2.355	1	0.125	0.04	0.001	2.439
LA/Ao	− 3.496	2.202	2.520	1	0.112	0.03	0.000	2.271
LPA(m/s)	0.736	5.420	0.018	1	0.892	2.088	0.000	85,762.875

*Indicates parameters found to be statistically significant ($p < 0.05$)

Table 4 Results of univariate regression analysis of variables at postnatal age of 24 h

Variables	β	SE	Wald	df	p Value	OR	95%CI	
							Lower	Upper
EF	0.025	0.034	0.555	1	0.456	1.026	0.959	1.097
FS	0.032	0.044	0.534	1	0.465	1.033	0.948	1.125
E/A	4.707	2.558	3.388	1	0.066	110.755	0.737	16,646.885
E/E'	0.107	0.076	2.009	1	0.156	1.113	0.96	1.291
PDA size /weight (mm/kg)*	1.841	0.610	9.099	1	0.003	6.305	1.906	20.859
LVO(ml/kg.min)*	0.049	0.016	8.906	1	0.003	1.050	1.017	1.084
LVEDd(mm)	− 1.554	1.819	0.730	1	0.393	0.211	0.006	7.475
LA/Ao	1.104	1.969	0.314	1	0.575	3.017	0.064	143.194
LPA(m/s)	9.920	5.407	3.367	1	0.067	20,333.299	0.508	813,311,747.2
DAo*	22.101	20,096.485	0.000	1	0.999	3,965,256,485	0.000	–

*Indicates parameters found to be statistically significant ($p < 0.05$)

Table 5 Results of univariate regression analysis of variables at postnatal age of 48 h

Variables	β	SE	Wald	df	p Value	OR	95%CI	
							Lower	Upper
EF	0.040	0.050	0.638	1	0.424	1.041	0.943	1.149
FS	0.038	0.069	0.304	1	0.582	1.039	0.907	1.190
E/A	2.035	2.444	0.693	1	0.405	7.653	0.064	920.505
E/E'	0.057	0.055	1.062	1	0.303	1.059	0.95	1.18
PDA size/weight (mm/kg)*	1.777	0.569	9.752	1	0.002	5.912	1938	18.036
LVO(ml/kg.min)*	0.015	0.006	7.209	1	0.007	1.015	1.004	1.026
LVEDd(mm)	− 0.992	1.673	0.352	1	0.553	0.371	0.014	9.832
LA/Ao	4.370	2.338	3.494	1	0.062	79.069	0.809	7730.881
LPA(m/s)*	26.087	7.968	10.718	1	0.001	2.135E+11	35,219.833	1.294E+18
DAo*	− 3.135	0.843	13.844	1	0.000	23.000	4.410	119.960

*Indicates parameters found to be statistically significant ($p < 0.05$)

difference in the incidence of pulmonary hemorrhage and BPD between the intervention group and non-intervention groups. This may be attributed to the small sample size used in our study. Furthermore, the presence of a PDA can result in systemic hypoperfusion that is associated with several morbidities, including hypotension and IVH, as confirmed by our study [4, 5, 10, 11].

Worthy of note is the fact that a significant shunt through the DA may remain clinically "silent" during the first few days of life [2, 12]. This is demonstrated in our study where

Table 6 Results of univariate regression analysis of variables at postnatal age of 72 h

Variables	β	SE	Wald	df	p Value	OR	95%CI Lower	95%CI Upper
EF	0.059	0.045	1.773	1	0.183	1.061	0.972	1.158
FS	0.068	0.056	1.459	1	0.227	1.071	0.958	1.196
E/A	3.120	2.221	1.972	1	0.16	22.639	0.291	1760.625
E/E'*	0.160	0.072	4.893	1	0.027	1.174	1.018	1.352
PDA size/weight (mm/kg)*	1.896	0.5 92	10.270	1	0.001	6.661	2.089	21.242
LVO(ml/kg.min)*	0.017	0.006	8.778	1	0.003	1.017	1.006	1.029
LVEDd(mm)	0.265	1.691	0.025	1	0.875	1.303	0.047	35.817
LA/Ao*	7.077	2.257	9.832	1	0.002	1183.942	14.199	98,717.018
LPA(m/s)*	18.038	6.270	8.276	1	0.004	68,217,631.55	313.726	1.483E+13
DAo*	3.353	0.907	13.674	1	0.000	28.600	4.836	169.153

*Indicates parameters found to be statistically significant ($p < 0.05$)

Table 7 Multivariable predictors of PDA that need to be treated with NSAIDs and/or surgical ligation in the predictive models

Model	Variables	β	SE	Wald	df	p Value	OR	95%CI Lower	95%CI Upper
Model 1	PDA size/weight at 0-12 h(mm/kg)	1.023	.496	4.248	1	0.039	2.782	1.052	7.360
	Intercept	−3.012	1.243	5.873	1	0.015	0.049		
Model 2	LVO at 24 h(ml/kg.min)	.049	.016	8.906	1	0.003	1.050	1.017	1.084
	Intercept	−11.862	3.800	9.745	1	0.002	0.000		
Model 3	PDA size/weight at 48 h(mm/kg)	1.777	0.569	9.752	1	0.002	5.912	1.938	18.036
	Intercept	−5.036	1.566	10.338	1	0.001	0.007		
Model 4	PDA size/weight at 72 h(mm/kg)	1.876	.649	8.357	1	0.004	6.530	1.830	23.305
	LA/Ao at 72 h	8.199	4.032	4.134	1	0.042	3635.779	1.343	9,839,607.803
	Intercept	−18.280	7.344	6.196	1	0.008	0.000		
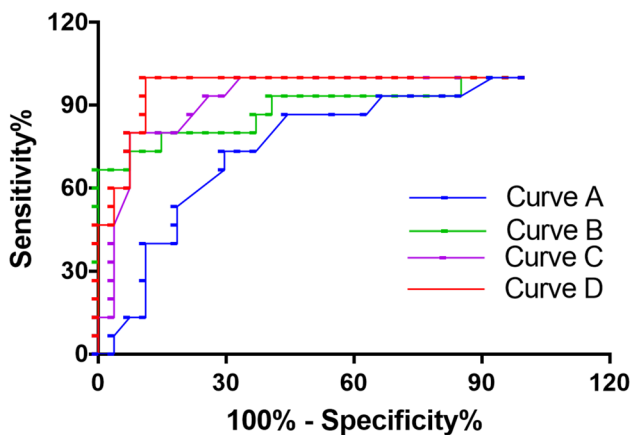
Fig. 2 Receiver operating characteristic curves (ROC) for predicting PDA that need to be treated with NSAIDs and/or surgical ligation. Curve A: PDA size/weight at postnatal age of 0-12 h; curve B: LVO at postnatal age of 24 h; curve C: PDA size/weight at postnatal age of 48 h; curve D: PDA size/weight and LA/Ao at postnatal age of 72 h

a lack of clinical evidence of hsPDA in the intervention group was accompanied by significant pulmonary overcirculation and systemic shunt effect within 72 h after birth, as identified using ultrasound indicators. Therefore, we used a combination of echocardiographic indices to construct a predictive model of PDA with a sensitivity and specificity of 100% and 88.9%, respectively. Consequently, our predictive model was helpful in predicting high risk of PDA requiring NSAIDs intervention and/or surgical ligation.

Transductal diameter has been identified as the most commonly used hsPDA indicator. Several clinical studies have identified transductal diameter as a risk factor for developing PDA [2, 13–15]. Transductal shunt volume is largely determined by the dimension of the shunt [16]. Clinical investigators have classified absolute PDA diameter into small (< 1.5), moderate (1.5–2.0), and large (≥ 2.0), respectively [17]. In the present study, we measured the diameter of ductus at its narrowest point corresponding to the pulmonary artery end, by direct view or color Doppler, and chose the ratio of diameter to patient's weight as the variable, instead of an absolute value. This option was considered because of the significant difference in birth weight between the two

groups in this study. In a previous study, L Storme found that the PDA size/weight > 1.4 mm/kg measured within 48 h after birth is a good indicator of hsPDA [18]. In addition, Kwinta reported that a PDA size/weight > 1.5 mm/kg measured 12–48 h after birth is a predictive index for PDA requiring surgical ligation [19]. Furthermore, Harling used PDA size/weight ≥ 2 mm/kg measured at 72 h of age as the predictive index for PDA requiring treatment [15]. However, our study found that PDA size/weight > 3.2 mm/kg at postnatal age of 72 h could be used as a predictive factor for infants with PDA requiring oral NSAIDs treatment and/or surgical ligation.

A large amount of transductal left-to-right shunt increases pulmonary blood flow and pulmonary venous return. Consequently, this increases the left-side heart volume loading, leading to dilatation of the left atrium and ventricle from increased preload, especially in the absence of a large intra-atrial shunt during the cardiovascular transition stage [20]. Hence, a ratio of LA/Ao can be used as a surrogate index of pulmonary overcirculation and hsPDA [21, 22]. Many previous clinical trials reported that LA/Ao ratio of > 1.5 is a predictor of hsPDA [2, 23, 24]. In our study, LA/Ao was obtained from the parasternal long-axis view using a plain 2D image and the final result is consistent with previous trials, demonstrating that LA/Ao > 1.4 at postnatal age of 72 h can be used as a risk factor for predicting PDA requiring treatment. Studies have demonstrated that LVO, which represents pulmonary blood flow, could be a predictive factor for hsPDA requiring intervention. High LVO value is often associated with a large left-to-right shunt through the PDA and pulmonary overcirculation [25]. A previous study reported that a cut-off of LVO > 300 ml/kg/min was associated with the clinical presence of hsPDA [2]. Another previous study demonstrated that the ratio of the LVO to superior vena cava flow is directly proportional to the ductus flow and, when ≥ 4, may indicate hemodynamic significance [26]. Our results show that LVO > 251.7 ml/kg.min at postnatal age of 24 h (sensitivity was 66.7%, specificity was 100%) could be used as a predictive factor for hsPDA requiring treatment.

The limitations of the present study are as follows: firstly, the indices of pulmonary overcirculation, such as LVEDd, end-diastolic velocity of LPA and mitral valve E/A, and systemic shunt effect such as retrograde blood flow of descending aorta during the first few days after birth, could not be used as risk factors to predict the necessity of therapy for PDA in our study. This is inconsistent with the results of some previous reports [27–29]. This inconsistency may be related to our sample size and needs further investigation. Secondly, in our study, we only used echocardiography indices as a predictor for PDA and did not include these clinical characteristics such as gestational age, birth weight, and the severity of RDS in the multivariate regression analysis.

Therefore, we are unable to determine whether there is a significant association between the need for PDA treatment and these clinical characteristics.

Conclusion

Serial daily echocardiographic assessment can be useful in predicting whether a PDA will be closed with NSAIDs and/or surgical ligation in preterm infants with gestational age ≤ 30 weeks.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Not applicable.

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