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Original Article

Investigation of echocardiographic characteristics and predictors for persistent defects of patent foramen ovale or patent ductus arteriosus in Chinese newborns

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ABSTRACT

Background: Persistent patent foramen ovale (PFO) and patent ductus arteriosus (PDA) increase the adult risk of cryptogenic embolic stroke and chronic pulmonary hypertension. To understand the characteristics of PFO and PDA in newborns, we investigated the spontaneous closure rate and derived the determinants for residual defects.

Methods: We utilized the database of congenital heart disease (CHD) in Xiamen ChangGung Memorial Hospital from 2015 to 2017 and allocated 2523 eligible newborns into four groups according to PDA, PFO, both or neither at birth. A total of 574, 1229, 202 and 518 newborns were assigned into the group of PFO and PDA, PFO alone, PDA alone and non-PFO/non-PDA, respectively. Regular echocardiographic follow-ups at baseline, 6, 12 and 24 months after

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Atrial septal defect
 Ventricular septal defect
 Spontaneous closure

birth were performed for evaluating the spontaneous closure rate in the subjects. Regression analysis was carried out to study the risk factors of residual congenital defects. Results: Newborns with PFO alone had the youngest birth age and lowest birth weight among the four groups. About one in four PDA-alone newborns had concomitant small ASD, i.e., <5 mm in diameter. Echocardiographic study showed that 71.3% and 30.8% of CHD newborns had PFO and PDA, respectively, compared to less than 10% of them having ASD or VSD. However, more than 95% of newborns with PFO or PDA closed spontaneously at 6 months, in contrast to about 30% of newborns with ASD or VSD had persistent existence of the intracardiac defects. Complex CHD significantly linked to persistent PFO or PDA at 6 and 12 months, with an adjusted hazard ratio of 9.03 (95% CI 1.97–41.46) and 12.11 (95% CI 2.11–69.72), respectively.

Conclusions: Chinese newborns with PFO or PDA expressed differences in characteristics and concomitant congenital defects. Additionally, persistent PFO or PDA is strongly associated with complex CHD and requires long-term regular monitoring for future associated complications.

At a glance of commentary

Scientific background on the subject

The risk of cryptogenic embolic stroke and chronic pulmonary hypertension is increased in adults with persistent patent foramen ovale (PFO) and patent ductus arteriosus (PDA), respectively. In this study, we tried to identify the echocardiographic characteristics of newborns who did not have spontaneous closure of PFO or PDA.

What this study adds to the field

The vast majority of PFO or PDA closed spontaneously at 6 months in the newborns with congenital heart disease (CHD). By contrast, one in three CHD newborns had persistent intracardiac defects. Of note, persistent existence of PFO or PDA is strongly associated with complex CHD and requires regular surveillance for long-term relevant complications.

Patent foramen ovale (PFO) and patent ductus arteriosus (PDA), two of congenital defects, are responsible for maintenance of intracardiac and extracardiac maternal-infant circulation, respectively [1–3]. Majority of normal newborns have spontaneous closure of PFO and PDA within 48 h after birth [4,5], except for those with congenital heart disease (CHD) in which these shunts are indispensable to maintain appropriate systemic oxygenation [6]. Not all of the newborns with CHD present with cyanosis, heart failure or failure to thrive, as long as these congenital defects are relatively small [7]. Sometimes, these small defects, especially small PFO, could not be found with neonatal ultrasound screening till progressive and obvious symptoms resulted from chronic volume or pressure overload in the adulthood [8]. On the contrary, more common congenital cardiac defects, such as atrial septal defect (ASD) or ventricular septal defect (VSD), are much easier found than PFO or PDA by neonatal or postnatal echocardiographic examination [9]. Data from previous studies have revealed that closure of ASD or VSD

depends on the defect size and neonatal and maternal age [10,11], whereas little is known about the determining factors of spontaneous PFO or PDA closure with time. Furthermore, as compared to ASD or VSD, there remained no clinical data regarding patients' characteristics when the newborns presenting with PFO or PDA. The relationship between PFO and PDA at birth and the coexistence of ASD or VSD is yet to be clarified, too.

Several literature reviews [12–14] have emphasized that residual PFO is strongly associated with cryptogenic embolic stroke which put the adult in danger of disabling life even though there were no other atherosclerotic risk factors identified. In addition, residual PDA increases pulmonary arterial blood flow, gradually leads to increment of right and left ventricular volume overload, acceleration of smooth muscle proliferation, and eventually progression into pulmonary hypertension (PHT) [15,16]. Unfortunately, compared to most symptomatic CHD that can be surgically repaired or percutaneously occluded early in their childhood or adulthood, asymptomatic persistent PFO and PDA have an increased risk of cryptogenic ischemic stroke and chronic PHT without any perceivable early warning signs. To find a way to early detect newborn with risk of persistent PFO or PDA and therefore, to maintain regular surveillance for the intracardiac and extracardiac shunts is necessary to reduce the future disabling disease burden. In this way, we intend to study characteristics of newborn with PFO and PDA at birth first, and then investigate the predictors of corresponding spontaneous closure.

Materials and methods

Study design and patient population

This is a retrospective cohort study performed at Xiamen ChangGung Hospital in southern China. We retrieved newborn and maternal data from CHD registry for this research (Number of institutional review board: XMCGIRB2018002). The database did not comprise newborns having severe complex

CHD with a need of cardiopulmonary resuscitation at birth or immediate surgical intervention, i.e., Apgar score less than or equal to 3 points. In addition, those expired shortly after birth without time for echocardiographic examinations also were not enrolled in the present study.

Since January 2015 through December 2017, a total of 2528 newborn were selected. After excluding 5 missing follow-up data, we allocated 2523 eligible patients into four groups according to the existence of PDA, PFO, both or neither at birth, namely, 574 newborns with coexistence of PFO and PDA, 1229 with PFO only, 202 with PDA alone, and remaining 518 with neither PFO nor PDA. Information regarding age, sex and birth weight of individual newborn and his/her maternal age was collected. Presentation of abnormal cardiac murmur and cyanosis was also recorded. Besides, whether prenatal cardiac anomalies on fetal ultrasound or neonatal extracardiac anomalies on routine newborn screening physical examination was also recorded based on the review of medical charts.

Definition and diagnosis

CHD was defined as cardiac structural problem that was present at birth [17]. Simple CHD lesions were defined as mild pulmonary valve stenosis, a small/uncomplicated ASD or VSD, PDA, and repaired ASD, VSD, PDA, and anomalous pulmonary venous connection without predominant residual shunt [18]. By contrast, complex CHD comprised any complex anatomical or physiological lesion as defined by the Bethesda conference [19]. Thus, in this study, those patients with combination of two or more congenital defects of cardiac valve, cardiac wall, or great vessels regardless of cyanosis were defined as “complex CHD”. We also defined extracardiac anomalies as hydrocephalus, microcephaly, holoprosencephaly, agenesis of the corpus callosum, Meckel-Gruber syndrome, esophageal atresia, duodenal atresia, diaphragmatic hernia, omphalocele, renal dysplasia, etc. Diagnoses of PFO, ASD, VSD, PDA, and complex CHD were entered in the registration system according to the results of neonatal echocardiographic examination. All of the echocardiographic findings and clinical presentation of cyanosis or cardiac murmur were further confirmed by a gynecologist and pediatrician.

Study purposes

We had several purposes to clarify through this retrospective CHD research. The first purpose was to understand the differences in baseline characteristics among newborns with PFO-alone, PDA-alone and concurrent existence of PFO and PDA at birth. The second one was to investigate the spontaneous closure rate of PFO, ASD, VSD, PDA, and complex CHD in the whole study cohort and the four groups. The last one was to further identify the independent predictors for spontaneous closure and persistent existence of PDA or PFO.

Monitoring and treatment for CHD

The candidates were admitted to newborn intensive care unit (ICU) for close monitoring and management if there was transient cyanosis or Apgar score between 4 and 7 points.

Oxygenation supply, intravenous fluid or parenteral nutrition support was applied depending on newborns' vital sign, clinical condition, and physiological need. In this research database, all newborns were cared and fed at newborn center 48 h after birth. Those who needed prolonged care at newborn ICU were not entered into the database and enrolled in the present study.

Echocardiographic measurement and regular follow-up time frame

We performed conventional 2-dimensional (2D) echocardiography with standard M-mode, tissue and color Doppler assessment, and 3D image for real-time reconstruction if any suspicious shunt or ambiguous diagnosis was encountered. Digital images were collected and data was analyzed based on the standardized protocol of the American Society of Echocardiography (<http://asecho.org/guidelines/guidelines-standards/>). Prenatal ultrasonic examination was performed by a gynecologist for screening fetal congenital anomalies. Neonatal echocardiography was done by a senior sonographer, experienced in congenital cardiovascular structural evaluation. The baseline echocardiographic study was performed as protocol at day 2 after birth, or immediately if there was an obvious cardiac murmur to auscultation on neonatal physical examination. If any abnormal shunt including aforementioned PFO, ASD, VSD, PDA or complex CHD was identified during hospitalization, the newborn with CHD would receive regular echocardiographic follow-ups at six, 12, and 24 months. The status of spontaneous closure of the congenital defects was evaluated by a pediatric physician and the results were recorded in the research database. Missing regular echocardiographic follow-up would be marked as data loss and excluded from denominator number in statistical analysis.

Clinical follow-up

Each newborn with congenital intracardiac or extracardiac defect received regular follow-up at pediatric outpatient clinic. The infant's mother was informed of the results of follow-up echocardiography and further educated regarding the care of the baby with CHD or keeping an alert on cyanosis and signs of heart failure. The necessity of follow-up was dependent on closure of these defects. Those infants with spontaneous closure did not require routine follow-up if general condition was acceptable. All data of follow-up were filed in a case report form and entered into registry after each clinical visit and on readmission for any event.

Statistical analysis

Data were expressed as mean \pm standard deviation (SD), percentage, or number, if appropriate. Continuous variables among four groups were compared with one-way ANOVA if normal distribution or Kruskal–Wallis analysis if normality is not satisfied. Additionally, categorical variables among groups were analyzed with chi-square test (or Fisher's exact). *P*-value was not reported if case number was less than 5. Categorical variables in different time points were compared with Cochran's Q test, followed by post-hoc comparison. For example, categorical variables at 6, 12, and 24 h, were

compared with Cochran's Q test, except for baseline one. In light of extremely significant spontaneous closure rate between baseline and 6-month follow-up for CHD, no baseline data was adopted as reference. Finally, to identify potential predictors for spontaneous closure of PFO/PDA or persistent PFO/PDA, logistic regression analysis was done to calculate the hazard ratio of individual variable for target outcomes. Statistical analysis was performed using SPSS statistical software for Windows ver. 22 (SPSS Inc., Chicago, IL, U.S.A.). *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics and echocardiographic findings among groups (Table 1)

Majority of newborns were born at mature age with optimal birth weight among all study cohorts. Mean maternal age was below thirty years old. About 4.5% of infants presented with cyanosis at birth but only half of them had obvious hypoxia. In addition, about 1% of subjects had intracardiac or extracardiac anomalies. Furthermore, PFO-alone newborns had the youngest age and lowest birth weight among four study groups (all *P* < 0.02). However, there were no significant differences in sex, maternal age, expression of cyanosis and hypoxia, and congenital anomalies among groups.

Regarding the baseline echocardiographic findings, PFO and PDA existed in about 7 and 3 of 10 newborns with CHD, respectively. Coexistence of PFO and ASD were very rare.

About 1 in 4 PDA-alone newborns had concomitant small ASD, i.e., <5 mm in diameter. Interestingly, PFO-alone group had significantly lower frequency of VSD as compared with that of PDA-alone counterpart. Besides, the rate of complex CHD was about 1% in all CHD newborn cohorts.

Echocardiographic follow-ups at 6, 12, and 24 months for the newborns with congenital cardiac defects (Table 2)

For all CHD newborns, part of congenital intra- and extra-cardiac defects disappeared within 2 years after birth. Although 71.3% and 30.8% of newborns had PFO and PDA, respectively, more than 95% of newborns with PFO or PDA closed spontaneously 6 months after birth. On the contrary, less than 10% of newborns had ASD or VSD, but these septal defects existed persistently in around 30% of the newborns 2 years later. Of note, closure rate of VSD in the PFO-alone group was lower than the whole cohorts (existence of VSD at 24 months: 20% vs. 10.7%). Also, PDA-alone group had a lower ASD closure rate as compared with all cohorts (existence of ASD at 24 months: 9.3% vs. 6.6%).

Predictors of spontaneous PFO or PDA closure (Table 3) and persistent existence of PFO or PDA (Table 4) at 6 and 12 months

Multivariate regression analysis revealed prenatal cardiac anomalies and complex CHD were predictive of persistence of PFO at 6- and 12-month echocardiographic follow-ups. However, although maternal age was associated with spontaneous

Table 1 Baseline characteristics among newborn groups allocated by existence of PFO, PDA, or not.

Variables	Overall (n = 2528)	PFO/PDA (n = 574)	PFO alone (n = 1229)	PDA alone (n = 202)	Non-PFO/non-PDA (n = 518)	<i>p</i> value
Background data						
Gender (male), % (n)	54.0% (1365)	52.7% (302)	54.3% (667)	55.0% (111)	54.8% (284)	0.889
Fetal age (week), mean ± SD	38.50 ± 1.85	38.46 ± 2.04 ^{a,b}	38.39 ± 1.94 ^a	38.62 ± 1.73 ^{a,b}	38.75 ± 1.40 ^b	0.023
≥37 weeks, % (n)	90.3% (2284)	89.7% (515)	88.9% (1093)	91.6% (185)	93.8% (486)	0.014
Birth weight (kg), mean ± SD	3196.8 ± 521.4	3213.7 ± 547.3 ^b	3154.0 ± 525.1 ^a	3234.5 ± 544.4 ^{a,b}	3265.0 ± 462.0 ^b	0.003
≥2500 gm, % (n)	91.2% (2306)	90.4% (519)	89.5% (1100)	93.6% (189)	95.2% (493)	0.001
Maternal age (year), mean ± SD	29.38 ± 4.20	29.07 ± 4.02	29.54 ± 4.23	29.08 ± 4.33	29.47 ± 4.21	0.117
≥35 years, % (n)	11.9% (301)	9.9% (57)	12.8% (157)	10.4% (21)	12.6% (65)	0.298
Cyanosis, % (n)	4.5% (114)	4.7% (27)	4.3% (53)	7.4% (15)	3.3% (17)	0.110
Cardiac murmur, % (n)	0.7% (18)	0.5% (3)	0.2% (3)	2.5% (5)	1.2% (6)	–
Hypoxia, % (n)	2.6% (66)	3.0% (17)	2.7% (33)	4.0% (8)	1.4% (7)	0.169
Family history of CHD, % (n)	0.1% (2)	0.2% (1)	0.0% (0)	0.0% (0)	0.2% (1)	–
Prenatal cardiac anomalies, % (n)	0.1% (2)	0.0% (0)	0.0% (0)	0.5% (1)	0.2% (1)	–
Neonatal extracardiac anomalies, % (n)	0.8% (19)	1.4% (8)	0.6% (7)	1.0% (2)	0.4% (2)	–
Echo findings at birth						
PFO, % (n)	71.3% (1803)	100% (574)	100% (1229)	0.0% (0)	0.0% (0)	–
PDA, % (n)	30.8% (776)	100% (574)	0.0% (0)	100% (202)	0.0% (0)	–
ASD, % (n)	9.8% (247)	1.2% (7)	0.1% (1)	38.1% (77)	30.7% (159)	<0.001
<5 mm, % (n)	7.7% (194)	0.3% (2)	0.1% (1)	27.2% (55)	25.7% (133)	<0.001
VSD, % (n)	3.4% (86)	2.3% (13)	1.9% (23)	5.9% (12)	7.2% (37)	<0.001
Complex CHD, % (n)	0.9% (22)	1.1% (6)	0.7% (8)	1.5% (3)	0.8% (4)	–

Data are expressed as mean ± standard deviation (SD) or percentage (number).

Difference in alphabetic characters (a, b) in superscript indicates statistical significance of *p*-value after comparison.

Abbreviations: PFO: patent foramen ovale; PDA: patent ductus arteriosus; CHD: congenital heart disease; ASD: atrial septal defect; VSD: ventricular septal defect; Echo: echocardiographic.

Table 2 Serial echocardiographic follow-up for CHD and comparison of frequency after six months.

Variables	Baseline	6 months	12 months	24 months	P value
Whole newborns (n = 2528)					
ASD, % (n)	9.8% (247)	27.5% (68) ^a	13.0% (32) ^b	6.5% (16) ^c	<0.001
PFO, % (n)	71.3% (1803)	5.0% (90) ^a	1.2% (22) ^b	0.4% (8) ^b	<0.001
PDA, % (n)	30.7% (776)	1.3% (10)	0.8% (6)	–	0.250
VSD, % (n)	3.4% (86)	30.2% (26) ^a	12.8% (11) ^b	9.3% (8) ^b	<0.001
PFO/PDA (n = 574)					
ASD, % (n)	1.2% (7)	14.3% (1)	0% (0)	0% (0)	–
PFO, % (n)	100% (574)	8.5% (49) ^a	1.6% (9) ^b	0.2% (1) ^b	<0.001
PDA, % (n)	100% (574)	0.7% (4)	0.5% (3)	–	1.000
VSD, % (n)	2.3% (13)	15.4% (2)	7.7% (1)	0% (0)	0.223
PFO alone (n = 1229)					
ASD, % (n)	0.1% (1)	0% (0)	0% (0)	0% (0)	–
PFO, % (n)	100% (1229)	3.3% (40) ^a	1.1% (13) ^b	0.6% (7) ^b	<0.001
PDA, % (n)	0% (0)	25.0% (1)	0% (0)	–	–
VSD, % (n)	1.9% (23)	39.1% (9) ^a	17.4% (4) ^b	17.4% (4) ^b	0.007
PDA alone (n = 202)					
ASD, % (n)	38.1% (77)	36.4% (28) ^a	18.2% (14) ^b	9.1% (7) ^b	<0.001
PFO, % (n)	0% (0)	0% (0)	0% (0)	0% (0)	–
PDA, % (n)	100% (202)	2.5% (5)	1.5% (3)	–	0.500
VSD, % (n)	59.4% (12)	25.0% (3)	8.3% (1)	0% (0)	0.097
Non-PFO/non-PDA (n = 518)					
ASD, % (n)	30.7% (159)	24.5% (39) ^a	11.3% (18) ^b	5.7% (9) ^b	<0.001
PFO, % (n)	0% (0)	2.0% (1) [*]	0.0% (0)	0.0% (0)	–
PDA, % (n)	0% (0)	0.0% (0)	0.0% (0)	–	–
VSD, % (n)	7.1% (37)	32.4% (12) ^a	13.5% (5) ^b	10.8% (4) ^b	0.001

Data are expressed as percentage (number). The fractions at 6, 12 and 24 months indicate number of congenital defects at 6-, 12- and 24-month follow-up divided by that at baseline, respectively.

Difference in alphabetic characters (a, b, c) in superscript indicates statistical significance of p-value after comparison.

*One child was incidentally found to have PFO that was not identified on the neonatal echocardiographic examination.

Abbreviations: ASD: atrial septal defect; PFO: patent foramen ovale; PDA: patent ductus arteriosus; VSD: ventricular septal defect; CHD: congenital heart disease.

closure of PDA at 6 months, no specific variable was found to link with PDA closure at 1 year because most of them closed by nature.

To further understand the persistent patency of PFO or PDA, newborns with nonspontaneous closure of PDA or PFA were retrieved and analyzed. After adjustment with multivariate analysis, maturity of fetus was identified to be protective against PFO or PDA persistence at 6 months. Prenatal cardiac anomalies including ASD were associated with persistent PFO or PDA at 12 months. Furthermore, complex CHD significantly linked to persistent PFO or PDA at 6 and 12 months, regardless of whether other intra- or extra-cardiac anomalies existed.

Discussion

This large-volume single-center retrospective cohort study investigating the Chinese newborns with PFO or PDA, two well-known risk factors for future cryptogenic embolic stroke and chronic PHT, yielded some striking clinical findings. First, the characteristics among groups allocated according to PFO, PDA, both or neither were diverse, e.g., PFO-alone newborns had the youngest birth age and lowest birth weight. Second, during 2-year follow-up period, spontaneous closure rates of PFO and PDA were much higher than those of ASD and VSD. Third, among Chinese newborns without spontaneous closure of congenital defects, those with PFO alone had lowest

VSD closure rate. On the contrary, those with PDA alone had lowest ASD closure rate. Finally, persistent PFO or PDA at 12 months was strongly associated with complex CHD in which there were more than two congenital defects over heart or great vessels.

A registered data of congenital cardiac malformation in Denmark [11] has shown the five-year spontaneous closure rates of ASD and VSD were about 70%, ranging from 20% for perimembranous VSD to 65% for isolated muscular VSD. In the present study by using CHD database from Chinese newborns, 2-year closure rates for ASD and VSD were around 90%. Thus, the racial difference in congenital cardiac defects between European and Asian population was predominant. However, the results implied that newborns with ASD or VSD had a high chance to close spontaneously without a need of surgical or catheter-based intervention if there is no obvious clinical complication or failure to thrive. As compared to the common septal defects, newborns with PFO or PDA had a much higher closure rate of more than 99% in our 2-year follow-up study, suggesting only one percent of them had persistent PFO or PDA. Whether paying attention to the residual defects is cost-effective by regular echocardiographic monitoring deserves further investigation. Besides, even with frequent follow-up of these defects, whether the risk of cryptogenic stroke and chronic PHT could therefore reduce also needs further study.

An interesting finding of our study was that 2-year spontaneous closure rate of ASD in the PDA-alone group was lower

Table 3 Identification of the predictors for spontaneous closure of PFO or PDA at 6 and 12 months.

Outcomes	Spontaneous PFO closure at 6 months (n = 1190)				Spontaneous PDA closure at 6 months (n = 197)			
	cHR (95% CI)	P value	aHR (95% CI)	P value	cHR (95% CI)	P value	aHR (95% CI)	P value
Gender (male)	0.79 (0.41–1.50)	0.466			1.86 (0.30–11.37)	0.503		
Fetal age (week)	1.14 (1.01–1.29)	0.037	1.15 (1.01–1.30)	0.031	0.94 (0.53–1.64)	0.817		
≥37 weeks	1.73 (0.75–3.99)	0.200			–	0.999		
Birth weight (kg)	1.00 (1.00–1.001)	0.393			1.00 (0.998–1.002)	0.912		
≥2500 gm	1.84 (0.80–4.25)	0.153			3.85 (0.40–37.22)	0.244		
Maternal age (year)	0.97 (0.90–1.04)	0.343			0.81 (0.67–0.999)	0.050	0.81 (0.67–0.999)	0.050
≥35 years	0.68 (0.29–1.56)	0.357			0.45 (0.05–4.24)	0.487		
cyanosis	0.86 (0.20–3.66)	0.836			–	0.999		
Cardiac murmur	–	0.999			–	0.999		
Family history of CHD	–	–			–	–		
Prenatal cardiac anomalies	0.08 (0.02–0.43)	0.003	0.09 (0.02–0.19)	0.004	–	1.000		
Neonatal extracardiac anomalies	–	–			–	1.000		
ASD at birth	–	1.000			0.40 (0.07–2.45)	0.323		
<5 mm	–	1.000			1.51 (0.17–13.82)	0.715		
VSD at birth	0.35 (0.08–1.52)	0.160			–	0.999		
Complex CHD at birth	0.53 (0.01–0.23)	<0.001	0.04 (0.01–0.19)	<0.001	–	0.999		

Outcomes	Spontaneous PFO closure at 12 months (n = 1207)				Spontaneous PDA closure at 12 months (n = 199)			
	cHR (95% CI)	P value	aHR (95% CI)	P value	cHR (95% CI)	P value	aHR (95% CI)	P value
Gender (male)	0.53 (0.16–1.72)	0.287			–	0.996		
Fetal age (week)	1.13 (0.92–1.40)	0.251			0.99 (0.50–1.93)	0.965		
≥37 weeks	2.42 (0.66–8.91)	0.183			–	0.999		
Birth weight (kg)	1.00 (0.999–1.001)	0.882			1.00 (0.997–1.002)	0.701		
≥2500 gm	1.55 (0.34–7.05)	0.574			–	0.999		
Maternal age (year)	1.10 (0.96–1.27)	0.169			0.83 (0.65–1.08)	0.162		
≥35 years	–	0.996			–	0.998		
cyanosis	0.54 (0.07–4.23)	0.558			–	0.999		
Cardiac murmur	–	0.999			–	0.999		
Family history of CHD	–	–			–	–		
Prenatal cardiac anomalies	0.02 (0.004–0.13)	<0.001	0.02 (0.003–0.11)	<0.001	–	1.000		
Neonatal extracardiac anomalies	–	–			–	1.000		
ASD at birth	–	1.000			0.30 (0.03–3.39)	0.332		
<5 mm	–	1.000			–	0.997		
VSD at birth	–	0.998			–	0.999		
Complex CHD at birth	0.03 (0.005–0.15)	<0.001	0.02 (0.004–0.13)	<0.001	–	0.999		

Abbreviations: PFO: patent foramen ovale; PDA: patent ductus arteriosus; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval; CHD: congenital heart disease; ASD: atrial septal defect; VSD: ventricular septal defect.

than that in the remaining 3 group. Also, the PFO-alone group had the lowest 2-year spontaneous closure rate of VSD among the 4 groups. So far, we did not find too much relevant information regarding ASD or VSD closure rate in specific CHD subgroup. Different to a previous Chinese study showing that PDA affects spontaneous closure of VSD [20] under 3 years of age, our study indicated that persistent PFO was associated with VSD. By contrast, a recent research from Taiwan [21] demonstrated that persistent VSD is negatively correlated with spontaneous closure of PFO and the result was compatible with our present finding. Therefore, the aforementioned issues regarding association between PDA or PFO versus ASD or VSD remain inconclusive at present. According to the predictors identified for persistent PFO or PDA, we assumed those newborns with complex CHD, i.e., more than two combined congenital defects, need these congenital shunts for maintenance of systemic circulation. Their presentations were quite different from critical CHD in which the infants require

surgery or catheter-based intervention in the first year of life [22]. Thus, delaying closure of the intra- or extra-cardiac shunt(s) keeps their survival for more than two years without advanced intervention for correction of the malformation.

In the current registered CHD database, we did not enroll those cyanotic newborns with severe complex or critical CHD with a need of cardiopulmonary resuscitation or early surgical intervention, because we intended to study the characteristics of Chinese newborns with PFO or PDA who might be under the risk of stroke or PHT in the future. As compared with simple CHD, those infants with complex CHD at baseline had higher risk for persistent PFO or PDA at 1 year during follow-up period, implying unclosed PFO or PDA might be associated with occult complex CHD. The phenomenon could be explained why there was more hypoxia noted in the PFO ± PDA groups compared with non-PFO/non-PDA group at baseline. The symptoms of heart failure or cyanosis may

Table 4 Identification of the predictors for persistent PFO or PDA at 6 and 12 months.

Outcomes Variables	Persistent PFO or PDA at 6 months (n = 96)				Persistent PFO or PDA at 12 months (n = 28)			
	cHR (95% CI)	P value	aHR (95% CI)	P value	cHR (95% CI)	P value	aHR (95% CI)	P value
Gender (male)	1.12 (0.72–1.73)	0.619			1.04 (0.49–2.22)	0.923		
Fetal age (week)	0.84 (0.77–0.92)	<0.001	0.83 (0.76–0.91)	<0.001	0.89 (0.77–1.03)	0.106		
≥37 weeks	0.36 (0.20–0.66)	0.001			0.65 (0.22–1.95)	0.442		
Birth weight (kg)	0.99 (0.99–1.00)	<0.001			1.00 (0.99–1.01)	0.723		
≥2500 gm	0.28 (0.16–0.49)	<0.001			0.89 (0.26–3.03)	0.846		
Maternal age (year)	1.04 (0.99–1.10)	0.107			0.97 (0.88–1.07)	0.507		
≥35 years	1.58 (0.83–2.98)	0.161			–	0.997		
cyanosis	1.94 (0.80–4.71)	0.146			0.75 (0.10–5.73)	0.781		
Cardiac murmur	–	1.000			–	1.000		
Family history of CHD	–	1.000			–	1.000		
Prenatal cardiac anomalies	2.33 (0.59–9.16)	0.227			5.23 (1.06–25.87)	0.043	6.06 (1.21–30.21)	0.028
Neonatal extracardiac anomalies	–	–			–	–		
ASD at birth	4.10 (0.90–18.60)	0.068			10.54 (1.85–60.18)	0.008	12.11 (2.11–69.72)	0.005
<5 mm	2.68 (0.24–29.90)	0.422			–	–		
VSD at birth	2.43 (0.73–8.04)	0.147			2.00 (0.25–16.23)	0.515		
Complex CHD at birth	7.33 (1.62–33.31)	0.010	9.03 (1.97–41.46)	0.005	10.48 (1.84–59.86)	0.008	12.11 (2.11–69.72)	0.005

Abbreviations: PFO: patent foramen ovale; PDA: patent ductus arteriosus; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval; CHD: congenital heart disease; ASD: atrial septal defect; VSD: ventricular septal defect.

progress with infant's growth. Extrapolating the strong association between complex CHD at birth and persistence of PFO or PDA at 12 months to clinical observation, complex CHD might closely link to longer nonspontaneous closure of PFO or PDA in the lifetime. As a result, the findings from the present study highlighted Chinese children with complex CHD should be regularly monitored not only for the progression of chronic PHT but also for the potential risk of cryptogenic stroke.

Aside from complex CHD, extracardiac anomalies, especially some established hereditary syndromes, have been found to be associated with multiple intra- and extra-cardiac malformation or defects [23,24]. However, the frequency of extracardiac anomalies in this Chinese population-based study was low, i.e., about 1%, and therefore multivariate analysis did not reveal significance in association between persistence of PFO or PDA and extracardiac anomalies. Because several literature have reported the newborns with obvious extracardiac deformation or syndrome usually have concomitant other cardiovascular malformation [25,26], pediatricians would pay more attention to the patients with extracardiac anomalies than undiagnosed complex CHD, highlighting our findings of strong link between complex CHD at birth and persistence of PFO or PDA. To keep regular surveillance of possible associated future complications is mandatory, especially for cryptogenic stroke and gradually developed asymptomatic PHT.

This study has some limitations. First, this is a research using a database from a tertiary medical center in China. Second, only newborns with identifiable CHD were entered into the database, and therefore those with normal echocardiographic findings and critical CHD were not enrolled. This might cause selection bias at baseline. Third, we only followed up patients with CHD at outpatient clinic till closure of congenital defects, so those without a need of follow-up were assumed as normal population. This might result in some deviation of final results due to less study population at the end of study.

Conclusion

In conclusion, despite high spontaneous closure rate for these common CHD, newborns with PFO or PDA have many differences in characteristics and concomitant congenital intra- or extra-cardiac defects. Complex CHD found at birth strongly links to persistent PFO or PDA at 6 months and 1 year, and needs regular follow-up for future relevant complications such as cryptogenic stroke or PHT.

Conflicts of interest

All authors report no conflicts of interest.

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