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Original Article

Factors influencing the spontaneous closure of ventricular septal defect in infants

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Abstract: This study is to prospectively evaluate the potential value of maternal and infantile variables as predictors for the spontaneous ventricular septal defects (VSD) closure in infants. Methods: Consecutive infants less than six-month-old when diagnosed with VSD, were followed-up for at least 5 years. Demographic, clinical and maternal factors were evaluated for the possible associations of the incidence of spontaneous VSD closure Of the 425 eligible infants, 93 had spontaneous VSD closure, 78.50% of which occurred when the patients were under 3 years of age. Diameter of the defect (D_{VSD}), ratio between diameter of the defect and aortic root diameter (D_{VSD}/D_{AR}), left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, infection scores, shunt ratio (Qp/Qs), VSD locations, and comorbidities including patent ductus arteriosus (PDA), and membranous septal aneurysm were independent predictors of spontaneous closure. However, maternal factors during the first 3 months of pregnancy and VSD infants with Down syndrome did not affect the spontaneous closure of infants with VSD. Conclusion: D_{VSD}, D_{VSD}/D_{AR}, left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, infection scores, Qp/Qs, VSD location, comorbidities including PDA, or membranous septal aneurysm may be used as potential independent predictors of spontaneous VSD closure in infants.

Keywords: Ventricular septal defect, spontaneous closure, predictive factor, prognosis

Introduction

Ventricular septal defect (VSD) is the most common congenital heart defect, which accounts for 20%-42.86% of all congenital heart diseases (CHD) [1-3]. The incidence of VSD is approximately 1.35 to 17.3 per 1000 live births [4, 5]. Some of these defects can close spontaneously, or diminish without surgical intervention [6]. However, some patients will suffer from complications such as growth retardation, recurrent infections, congestive heart failure, and even sudden death [7]. Therefore, it is very important for pediatricians to decide whether the infants with VSD need surgical intervetions, and even more importantly, when these interventions should be performed.

A few recent studies have investigated the prognosis related factors in patients with VSD. Factors such as size [8] and location [9-13] of the defects, ages of diagnosis [8, 14], and the presence of membranous septal aneurysm [6, 15, 16] have been identified as predictors of spontaneous closure. In addition, ratio of VSD area to body surface area [15], ratio between diameter of the defect to aortic root diameter (D_{VSD}/D_{AR}) [17], shunt ratio (Qp/Qs) [6], as well as comorbidities of congestive heart failure (HF) [9, 18] have also been evaluated. Shiral et al [16] chose the most comprehensive clinical and morphometric features to predict spontaneous VSD closure in individual patients, and found that factors including chromosomal anomalies, ethnicity, gender, family history of CHD, and left ventricular fractional shortening were not significantly associated with frequency of spontaneous closure. However, the results of the above studies were not always consistent, possibly due to relatively short length of the follow-up period, small sample sizes, wide age spans of VSD diagnosis, and incomprehensive potential prognostic factors analyzed. Therefore, studies are warranted to quantitatively estimate the reliable predictors of spontaneous VSD closure in infants. The current study

is designed to prospectively evaluate the potential value of maternal and infantile variables as predictors for the spontaneous VSD closure in infants.

Methods

Patients

Five hundred and forty consecutive patients who were less than six-month-old (from 1 day to 6 month, 65 ± 21 days, mean ± SD), weight from 2.1 kg to 10.1 kg, 4.3 ± 0.6 kg, mean ± SD, and had been diagnosed as VSD by echocardiography in the First Affiliated Bethune Hospital of Jilin University between January 2000 and June 2008, were included in the current study. These patients were followed clinically and echocardiographically for at least 5 years. The follow-up was terminated when spontaneous closure of the VSD occurred. Eighty-four patients were not included into the analyses because they were lost during follow-up or received surgical closure of VSD. We also did not include 31 cases of VSD children with complex congenital heart disease in the natural healing analysis. However, due to the relative large number of these cases, we still kept to follow-up. Thus, 425 patients were included in the final analyses. This study has been approved by the Ethics Committee of Jilin University School of Medicine, and the parental consents were obtained for each infant.

Definitions of related variables and outcomes

Scores of infection [17] were defined as 1 point if the patient was diagnosed with comorbidities of bronchitis and as 2 points if the patient was diagnosed with pneumonia and infections lasted more than 2 weeks. Severity of HF was evaluated according to the modified Ross grading score of pediatric HF [19], specifically 3-6 points for mild HF, 7-9 points for moderate HF, and 10-12 points for severe HF. Diagnostic criteria of pulmonary hypertension were defined as pulmonary artery systolic pressure (PASP) between 36 and 50 mm Hg [20], or mean pulmonary artery pressure (MPAP) > 25 mm Hg [21]. Diagnostic criteria for children with anemia [22] were defined as serum blood hemoglobin < 145 g/L (neonates), < 90 g/L (infants of 1-4 months), and < 100 g/L (4-6 months infants). Spontaneous closure of a VSD was defined as meaningless or functional murmur, absence of a previously audible systolic murmur, absence of a previously documented defect by two-dimensional imaging, and absence of flow across the ventricular septum by color flow Doppler mapping or cardiovascular angiography. Heavy drinking [23] of a pregnant woman was defined as 4 or more standard drinks in a day, or more than 15 standard drinks in a week, in which 1 standard drink is equivalent to any wine containing 14 grams of alcohol. Smoking for a pregnant woman [24] was defined as smoking index > 100 (number of cigarettes smoked per day × years of smoking).

Demographic and clinical data

The following demographic and clinical data were collected: 1) Ages of first diagnosis of VSD; 2) Presence of other congenital diseases, such as chromosomal defects; 3) Presence of other CHD, such as patent ductus arteriosus (PDA), atrial septal defect (ASD), pulmonary hypertension, etc; 4) Presence of other complications, such as hyperbilirubinemia and anemia, etc; 5) Incidence of heart failure or respiratory infection; 6) Defect closure with the longest follow-up duration; and 7) Undergoing surgical or interventional repair for VSD.

Maternal risk factors during the first 3 months of pregnancy

The following maternal variables were collected: 1) heavy drinking or smoking; 2) sickness (record the name of the drug administered if any); and 3) X-ray exposure.

Echocardiographic parameters

Echocardiography was performed by two experts. Sedation with chloral hydrate, administered by enema, was used when necessary. All the parameters were obtained with TOSHIBA SSH-880CV echocardiography ultrasound (Tokyo, Japan). Echocardiograms were performed with 3-MHz transducers appropriate for the patient's size. Standard parasternal long-axis, short-axis and 4-chamber view, 5-chamber view plus subcostal sagittal and coronal views were obtained. A typical systolic color flame crossing the septum and a jet derived from continuous Doppler were considered diagnostic for VSD (the maximum and minimum diameter). Each parameter was measured twice by different operators, and the mean data was used for

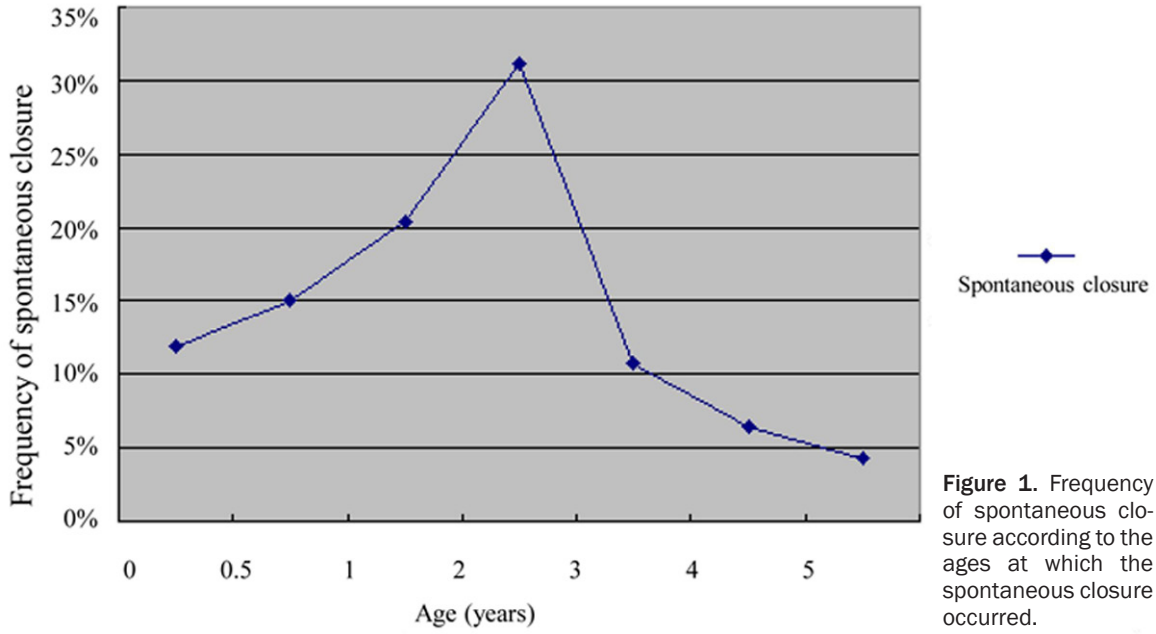

Figure 1. Frequency of spontaneous closure according to the ages at which the spontaneous closure occurred.

analysis. The following echocardiographic parameters were recorded at the first diagnosis of VSD: 1) D_{VSD} [(maximum diameter + minimum diameter)/2], categories of VSD according to the location [perimembranous, muscular, subarterial, or mixed-type(including two of the above three types)], aortic inner diameter, main pulmonary forward blood flow, left atrial sizes, right ventricular sizes, left ventricle sizes, interventricular septal thickness, and peak forward flow velocity of aortic and pulmonary artery; 2) ratio between the diameter of the defect and the aortic root diameter (D_{VSD}/D_{AR}); and 3) Qp/Qs (pulmonary artery diameter/aortic diameter)^2 × (pulmonary artery velocity time integral / aortic velocity time integral).

Statistical analysis

Continuous variables were presented as means ± standard deviations, and dichotomous variables were presented as percentages. Statistical analyses were performed with SPSS 17.0 software. *P* values less than 0.05 (2-tailed) were considered statistically significant. Ages at which spontaneous VSD closure occurred were grouped as 0 to 6 months, ~1 year, ~2 years, ~3 years, ~4 years, ~5 years, and > 5 years. The frequencies of spontaneous closure within each age group, as well as the distribution of patients with spontaneous VSD closure according to the age groups were calculated, respectively. Chi-squared exact tests and student t-tests were used to compare the differences between the discrete and continuous variables. Multivariate logistic regression analyses were performed to identify the potential independent predictors of spontaneous closure. Bivariate logistic regression analyses were used to compare the differences between the incidences of spontaneous closure according to the location of VSD. The receiver operating characteristic curve (ROC) analyses were applied to estimate the most appropriate cutoff value (the maximum value of sensitivity plus specificity) of the continuous variables for the prediction of spontaneous closure.

The variables included in the logistic analyses were D_{VSD}, D_{VSD}/D_{AR}, aortic inner diameter, main pulmonary artery diameter, left atrium sizes, left ventricle sizes, right ventricle sizes, interventricular septal thickness, main pulmonary forward blood flow, infection scores, Qp/Qs, location of VSDs, comorbidities including PDA, membranous septal aneurysm, Down sydrome, pulmonary hypertension, anemia, hyperbilirubinemia, and maternal factors such as heavy drinking, smoking, drug administration, and X-ray exposure within the first three months of pregnancy.

Results

Baseline demographic characteristics

Four hundred and twenty-five patients, of which 258 (60.7%) were boys and 167 (39.3%) were girls, were included in the analyses. Spon-

Table 1. Differences of echo results between patients with and without spontaneous closure of ventricular septal defects

Variables	Spontaneous closure group	None spontaneous closure group	*P* value
Diameter of the defect (mm)	2.96 ± 1.37	7.23 ± 1.39	0.000
Aortic inner diameter (mm)	12.34 ± 4.08	13.54 ± 3.96	0.315
Diameter of the defect/aortic root diameter	0.25 ± 0.03	0.62 ± 0.09	0.000
Main pulmonary artery diameter (mm)	12.21 ± 3.15	16.49 ± 3.42	0.000
Left atrium sizes (mm)	15.06 ± 4.67	18.27 ± 4.49	0.000
Right ventricle sizes (mm)	11.79 ± 3.42	12.16 ± 3.68	0.387
Left ventricle sizes (mm)	24.33 ± 6.22	29.26 ± 6.67	0.000
Interventricular septal thickness (mm)	3.76 ± 1.20	4.08 ± 1.25	0.141
Main pulmonary forward blood flow (cm/s)	1.13 ± 9.83	1.59 ± 9.72	0.018
Shunt ratio (Qp/Qs)	1.12 ± 0.12	2.15 ± 0.19	0.000
Patients with atrial septal defect, n (%)	34 (36.56)	133 (40.06)	0.529
Patients with patent ductus arteriosus, n (%)	7 (7.53)	51 (15.36)	0.011
Patients with pulmonary hypertension, n (%)	3 (3.23)	18 (5.42)	0.406
Patients with membranous septal aneurysm, n (%)	23 (24.73)	22 (6.62)	0.000
VSD locations			
Perimembranous, n (%)	75 (80.64)	238 (71.69)	0.000
Muscular, n (%)	18 (19.35)	35 (10.54)	0.000
Subarterial, n (%)	0 (0)	39 (11.75)	0.000
Mixed-type, n (%)	0 (0)	20 (6.02)	0.000

taneous VSD closure occurred in 93 (21.88%) of the 425 patients during the follow-up. According to the defect locations, VSDs were classified as perimembranous (n = 313, 73.65%), muscular (n = 53, 12.47%), subarterial (n = 39, 9.18%), and mixed-type (n = 20, 4.70%). The following complications were noted in the study cohort: ASD (n = 167, 39.29%), PDA (n = 58, 13.65%), pulmonary hypertension (n = 21, 4.94%), membranous septal aneurysm (n = 45, 10.59%), Down's syndrome (n = 26, 6.12%), hyperbilirubinemia (n = 104, 24.47%), and anemia (n = 37, 8.71%). Not any children with comorbidities of complex CHD patients occurred spontaneous closure.

Frequency of spontaneous closure based on the ages of the included infants

As shown in **Figure 1**, the frequencies of spontaneous VSD closure according to the ages of patients were classified as < 6 months (n = 11, 11.83%), ~1 year (n = 14, 15.05%), ~2 years (n = 19, 20.43%), ~3 years (n = 29, 31.19%), ~4 years (n = 10, 10.75%), ~5 years (n = 6, 6.45%), and > 5 years old (n = 4, 4.30%). Up to 78.50% of the whole spontaneous closure events occurred when the patients were under 3 years old; whereas, frequency of spontaneous closure decreased sharply after the first 3 years of life.

Differences of baseline characteristics between patients with and without spontaneous VSD closure

As shown in **Tables 1**, **2**, the following variables were significantly different and could be identified as potential predictors of spontaneous closure by Student t-test and chi-squared test: D_{VSD}, D_{VSD}/D_{AR}, main pulmonary artery diameter, left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, Qp/Qs, VSD locations, and patients with PDA, membranous septal aneurysm, lung infection scores, Down's syndrome, and anemia. No significant differences were detected (*P* all > 0.05) in aortic inner diameter, right ventricle sizes, interventricular septal thickness, patients with ASD, pulmonary hypertension, hyperbilirubinemia, and maternal factors (heavy drinking or smoking, drug administration, and X-ray exposure during the first 3 months of pregnancy) between those with and without spontaneous VSD closure.

Table 2. Differences of other potential determinants between patients with and without spontaneous closure of ventricular septal defects

Infection scores	2.20 ± 0.82	3.01 ± 1.02	0.000
Patients with Down syndrome, n (%)	1 (1.08)	25 (7.53)	0.025
Patients with hyperbilirubinemia, n (%)	19 (20.43)	85 (25.60)	0.058
Patients with anemia, n (%)	3 (3.23)	34 (10.24)	0.019
Maternal factors during the first 3 months pregnancy			
Heavy smoking, n (%)	19 (20.40)	84 (25.30)	0.058
Heavy drinking, n (%)	17 (18.28)	80 (24.10)	0.060
Drug administration, n (%)	24 (25.81)	102 (30.70)	0.069
X-ray exposure, n (%)	13 (13.98)	64 (19.28)	0.064

Table 3. Prediction of spontaneous closure by multivariate regression analysis

Variables	Odds ratio	95% confidence interval	*P* value
Diameter of the defect	0.402	0.317-0.605	0.000
Diameter of the defect/aortic root diameter	0.323	0.206-0.573	0.000
Left atrium sizes (mm)	0.582	0.415-0.713	0.034
Left ventricle sizes (mm)	0.513	0.334-0.627	0.021
Main pulmonary forward blood flow (cm/s)	0.529	0.397-0.663	0.027
Infection scores	0.458	0.314-0.619	0.000
Shunt ratio (Qp/Qs)	0.389	0.224-0.519	0.000
Patients with patent ductus arteriosus	0.613	0.449-0.753	0.038
Patients with membranous septal aneurysm	1.552	1.294-1.684	0.000
Location of VSDs			
Perimembranous	1.434	1.295-1.611	0.000
Muscular	1.440	1.318-1.707	0.000
Subarterial	0.418	0.304-0.605	0.000
Mixed-type	0.401	0.285-0.590	0.000

Prediction of spontaneous VSD closure: results of multivariate regression analysis

Multiple logistic regression analysis was performed to identify independent predictors of spontaneous VSD closure in this cohort. As shown in **Table 3**, of the 13 candidate variables, D_{VSD}, D_{VSD}/D_{AR}, left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, infection scores, Qp/Qs, VSD locations (perimembranous, muscular, subarterial, or mixed-type), conorbidities of PDA, and membranous septal aneurysm were found to be independent predictors of spontaneous closure (P all < 0.05).

Prediction of spontaneous closure according to the locations of VSDs: results of bivariate regression analysis

To further compare the impact of defect locations on the incidence of spontaneous VSD closure, bivariate regression analysis was performed. As shown in **Table 4**, significant differences of incidence of spontaneous closure ($P < 0.05$) were detected between patients with perimembranous and subarterial or mixed-type VSD, as well as patients with muscular versus subarterial or mixed-type defects. However, no significant ($P > 0.05$) differences were detected in patients with perimembranous and muscular defects, and between those with subarterial and mixed-type defects.

Determination of the cutoff values of continuous variable for the prediction of spontaneous VSD closure: results of ROC analyses

As shown in **Table 5**, ROC curve analyses indicated that the most appropriate cutoff values for D_{VSD}, D_{VSD}/D_{AR}, left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, lung infection scores, and Qp/Qs were 2.85 mm, 0.23, 19.5 mm, 32.5 mm, 1.01 cm/s, 2.43,

Table 4. Prediction of spontaneous closure of defects locations by bivariate regression analysis

Location of VSDs	Odds ratio	*P* value
Perimembranous versus muscular defects	1.402	0.626
Perimembranous versus subarterial defects	0.045	0.012
Perimembranous versus mixed-type defects	0.036	0.006
Muscular versus subarterial defects	0.038	0.002
Muscular versus mixed-type defects	0.025	0.001
Subarterial versus mixed-type defects	0.839	0.915

and 1.53, respectively, to predict the incidence of spontaneous VSD closure. The cutoff values for these variables were 5.2 mm, 0.56, 26 mm, 37.5 mm, 2.01 cm/s, 3.16, and 2.12, respectively, for the prediction of spontaneous closure

Discussion

In this study, we explored the potential clinical and echocardiographic predictors of spontaneous VSD closure for infantile patients. Results of our study showed that D_{VSD}, D_{VSD}/D_{AR}, left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, infection scores, Qp/Qs, VSD location, and comorbidities including PDA, and membranous septal aneurysm were independently associated the incidence of spontaneous VSD closure in these patients.

A variety of factors have been found to affect the incidence of spontaneous VSD closure. Age at which VSD was diagnosed was one of the most common factors shown to affect the incidence of VSD closure. Results of several studies have suggested that spontaneous VSD closure primarily occurred in the first 2 years of life [25], or within the adolescent period [6, 16]. In our study, spontaneous closure of VSDs during the first 3 years accounted for up to 78.50% of all spontaneous closure events, and the incidence of spontaneous closure decreased sharply after four years of age. However, due to the small sample sizes and relatively short follow-up duration of our study, long-term incidence of spontaneous VSD closure needs to be further evaluated in future studies.

The size of VSD has also been considered as another important factor, which was independently associated with the spontaneous closure in patients with VSDs. D_{VSD} was the most commonly used parameter to assess the extent of VSD. Our results indicated that the incidence of spontaneous closure was inversely related to D_{VSD}, and a higher possibility of spontaneous closure can be observed in patients with D_{VSD} was less than 2.85 mm. On the contrary, spontaneous VSD closure rarely occurred in patients with D_{VSD} more than 5.2 mm. However, some suggested that D_{VSD} may be too simple to reflect the severity of the disease because many other factors, such as age, height, body weight, and defects type may influence severity [26], which potentially limited its application in the clinic. D_{VSD}/D_{AR} has been proposed to be a suitable variable to reflect the extent of shunting blood flow and the severity of VSD [17], since D_{VSD} has been adjusted to D_{AR} in this parameter. Our results showed that D_{VSD}/D_{AR} was an independent predictor for spontaneous closure in patients with VSD. We found higher D_{VSD}/D_{AR} ratios correlated with lower probabilities of spontaneous closure. Meanwhile, ROC curve analyses indicated that the incidence of spontaneous closure was higher in patients with D_{VSD}/D_{AR} ratio less than 0.23; conversely, VSD spontaneous closure rarely occurred in patients with D_{VSD}/D_{AR} more than 0.56.

VSD can be classified according to its location as follows: perimembranous VSD, muscular VSD, subarterial VSD and mixed-type VSD. Previous studies suggested that the incidence of spontaneous VSD closure may vary according to location. Spontaneous VSD closure mainly occurred in muscular and membranous defects, and patients with muscular defects had higher spontaneous closure than those with perimembranous defects [9, 12, 13]. Although our study also showed a relatively high incidence of spontaneous closure in patients with muscular and membranous VSD, no significant difference in spontaneous closure rates was observed between patients with muscular and membranous defects VSD ($P > 0.05$). This inconsistency could be partly explained by the small sample size of patients with muscular defects in our study. Our study also found that patients with subarterial and mixed-type VSD had a low incidence of spontaneous closure. Meanwhile, higher incidence of spontaneous closure can be found in patients with membranous septal aneurysm.

Table 5. Cutoff values of continuous variable related to spontaneous closure of ventricular septal defects

Variables	Cutoff values (Maximal sensitivityplus specificity)	Maximal sensitivity plus specificity (%)	Cutoff values (sensitivity as zero)
Diameter of the defect (mm)	2.85	78.3	5.2
Diameter of the defect/aortic root diameter	0.23	76.3	0.56
Left atrium sizes (mm)	19.5	71.9	26
Left ventricle sizes (mm)	32.5	81.2	37.5
Aortic and pulmonary artery forward velocity (cm/s)	1.01	74.1	2.01
Infection scores	2.43	73.5	3.16
Shunt ratio (Qp/Qs)	1.53	72.2	2.12

Quantitative assessments of the cardiac shunt have been widely used to assess the severity of VSD. Owing to the gap-effect of the ventricular septum, left ventricular systolic pressure was higher than that of the right ventricle. Thus, left-to-right interventricular shunting occurred in patients with VSD, leading to increase of pulmonary blood volume and pulmonary artery flow, and finally, pulmonary congestion. Therefore, these patients are usually associated with recurrent pulmonary infection, reduced physical tolerance, and presence of HF. Additionally, large amount of left-to-right interventricular shunting may result in pulmonary arteriolar spasm, and further induce dynamic pulmonary hypertension. With the progression of the disease, secondary pulmonary arterial intimal thickening and hardening may occur, eventually resulting in resistant pulmonary arterial hypertension. Gabriel et al [14] indicated that surgical closure was not necessary during childhood as long as Qp/Qs was less than 2, the size of the left ventricle was normal, and pulmonary hypertension or aortic regurgitation were absent. Results of our study not only confirmed this perspective, but also demonstrated that parameters including the left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, lung infection scores, as well as Qp/Qs all independently influenced the spontaneous VSD closure. Higher values associated with these afore mentioned variables are correlated with lower probability of VSD closure.

Results of ROC analyses indicated that spontaneous VSD closure likely to happen in patients with the left atrium sizes < 19.5 mm, left ventricle sizes < 32.5 mm, main pulmonary forward blood flow < 1.01 cm/s, infection scores < 2.43, or Qp/Qs < 1.53; conversely, spontaneous VSD closure rarely happened in patients with the left atrium sizes > 26 mm, left ventricle sizes > 37.5 mm, main pulmonary forward blood flow > 2.01 cm/s, infection scores > 3.16, or Qp/Qs > 2.12. Higher values reflected more left-to-right interventricular shunting and more serious hemodynamic abnormalities, thus led to a lower chance of spontaneous closure. Although pulmonary hypertension was not found to be an independent predictor for spontaneous closure in the current study, we did find that VSD patients with pulmonary hypertension had a lower incidence of spontaneous closure compared to those without pulmonary hypertension. The lack of statistical significance may be explained by the fact that the number of VSD patients with pulmonary hypertension was small in our study. Further studies with larger sample sizes of VSD patients with pulmonary hypertension are warranted.

VSD is often presented with other congenital or acquired diseases, including other congenital heart diseases, chromosome diseases, anemia and hyperbilirubinemia. No previous studies, to the best of our knowledge, have addressed the issue whether VSD patients with other diseases affect spontaneous closure, besides Down's syndrome [15]. We analyzed the spontaneous VSD closure in patients with ASD, PAD, and Down's syndrome. The results showed that the incidence of spontaneous closure decreased in VSD patients with PDA. However, complications of ASD or Down's syndrome had little impact on the incidence of spontaneous closure. The fact that VSD patients with PDA had a low incidence of spontaneous closure may be because PDA further increased left-to-right shunt flow, and led to more severe hemodynamic abnormalities. As

for VSD patients with comorbidities of ASD, since no obvious pressure gradient was found between the left and right atrium, minimal changes in left-to-right shunt and related hemodynamic abnormalities could be detected. Although the results of chi-squared test indicated that VSD patients with Down's syndrome had a higher rate of spontaneous closure ($P = 0.032$), results of multivariate regression analysis did not support complication with Down's syndrome as a predictor for spontaneous closure. Whether the negative results were caused by the fact that there were a limited number of patients with Down's syndrome in our study need to be clarified in future studies. Furthermore, complications such as anemia or hyperbilirubinemia did not seem to affect the spontaneous closure in our study, possibly because these two acquired diseases had little impact on ventricular hemodynamic changes.

Most previous studies [27] have confirmed that heavy drinking or smoking during the first 3 months of pregnancy has an impact on the occurrence of CHD in the fetus. However, no study has evaluated the impact of maternal drinking or smoking on spontaneous closure in infants with VSD. Our analysis showed that maternal factors, such as heavy drinking, smoking, drug administration, and X-ray exposure during the first 3 months of pregnancy did not affect the spontaneous closure of infants with VSD ($P > 0.05$). These results may simply indicate that maternal life style cannot further affect the development of infants after birth.

Besides the echocardiographic and clinical features, some investigators have attempted to predict spontaneous VSD closure using some potential biomarkers. A positive trend between the severity of VSD and activities of metalloproteinases (MMP)-2 and MMP-9 was found in a recent report [28]. Notably, circulating MMP-9 could be an indicator of myocardial repair for patients with VSD [29]. Additionally, a preclinical study [30] showed that protein kinase B/Akt plays a critical role in the pathogenesis of heart defects of Akt1-deficient mice. Combining the echocardiographic and clinical features with these potential biomarkers may further improve our ability to predict spontaneous closure in patients with VSD.

As an observational study, there are some limitations to this study which needs to be considered when interpreting the results. It should be noted that the subjects were less than 6 years; there might be some spontaneous closure cases with mirror VSD or severe VSD cases undergoing repair surgery. This may affect the current results, but has little impact on the overall trend. First, the natural course of VSD is dynamic, and we only followed the change in echocardiographic features at intervals of one year after the first year of life. Therefore, the time of spontaneous closure may be a conservative estimate. Second, our study was a single-center study with a relatively small sample size in the subgroups, thus we could not exclude statistical bias. Third, we could not estimate the long-term (more than 5 years) incidence of spontaneous closure; however, a favorable long-term prognosis for children with VSD has been shown [14]. We will continue following these patients to observe the spontaneous closure outcome at advanced age. Fourth, although we have tried to collect more variables which potentially affect the spontaneous VSD closure, it is possible that some important variables may have been neglected. Finally, we did not summarize the surgical closure outcomes of VSD, which could also provide some additional information.

In conclusion, our study suggests that the main predictors for the probability of spontaneous closure in infants with VSD are cardiac structure and hemodynamic parameters. $D_{VS}D$, D_{VSD}/D_{AR}, left atrium sizes, left ventricle sizes, main pulmonary forward blood flow, infection scores, Qp/Qs, VSD location, and comorbidities such as PDA, and membranous septal aneurysm may be predictors of spontaneous closure in these patients. The most appropriate cutoff value of the continuous variables for the prediction of spontaneous closure is useful to the clinical work. But the maternal factors do not affect the spontaneous closure of infants with VSD. Notably, the impact of age cannot be ignored.

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Disclosure of conflict of interest

None.

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