

## Original Article

# Incidence and Disease Course of Isolated Ventricular Septal Defects Presenting in Infancy in Hong Kong

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### Abstract

**Introduction:** Ventricular septal defect is the most common congenital heart lesion in newborns. Incidence and natural history vary depending on the study method. Very few local studies are available. This study aims to provide information about the incidence, anatomical type and disease course including the spontaneous closure rate of isolated ventricular septal defects diagnosed in infancy in Hong Kong. **Methods:** Infants who were diagnosed to have isolated ventricular septal defects with echocardiography were followed to at least 6 years of age or till defect closure. Patients' demographics, clinical data, echocardiogram images and reports were reviewed and analysed. **Results:** 237 infants with isolated ventricular septal defects were identified. The incidence was 4.97/1000 live births. The spontaneous closure rate was 60% for all defects, 55% for perimembranous defects, 79% for muscular defects and 7% for subarterial defects. **Conclusion:** This study provided updated local information on the incidence, anatomical type, natural history, and spontaneous closure rate of ventricular septal defects diagnosed in infancy.

### Key words

Echocardiography; Heart septal defects, Ventricular; Incidence; Infant; Remission, Spontaneous

### Introduction

Ventricular septal defect (VSD) is the most common structural congenital heart disease in newborns. Previous studies reported an incidence ranging from 1.56 to 53.2 per 1000 live births.<sup>1-11</sup> A local study in 1996 reported that the incidence of VSD in Hong Kong was comparable to that in the West.<sup>12</sup> With the advancement and more widespread use of echocardiography and antenatal ultrasound, we expect more small defects would be diagnosed.

The natural history of isolated ventricular septal defects

(VSDs) remained debatable. Most early studies were conducted in tertiary centres, resulting in selection bias towards the inclusion of more clinically significant defects. Recent studies in the West found a spontaneous closure rate ranging from 20% to 82% for perimembranous VSD and 64% to 97% for muscular VSD at 5 to 6 years of life.<sup>4,5</sup> Studies in the Chinese population also reported similar findings, with spontaneous closure rate ranging from 24% to 57% for perimembranous VSD and 64% to 97% for muscular VSD respectively at 6 years of life.<sup>7,8,13</sup> The previous study in Hong Kong reported a spontaneous closure rate of only 18% and 60% for perimembranous VSD and muscular VSD respectively at 2 years of life.<sup>12</sup> There was no study on the long term spontaneous closure rate in the local population.

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### Study Objectives and Purpose

The present study aims to examine the incidence, anatomical type and disease course, including the

spontaneous closure rate of at least 6 years of age, of isolated ventricular septal defect diagnosed in infancy in a secondary hospital setting.

## Methods

The Department of Paediatrics and Adolescent Medicine of Pamela Youde Nethersole Eastern Hospital in Hong Kong provided medical care to patients with congenital heart disease at secondary level rather than tertiary level. The patients were either babies born in the hospital or referred from primary care providers such as Maternity and Child Health Centres or private doctors. Patients with date of birth between 1st January 2004 and 31st December 2014 with diagnostic code of ventricular septal defect managed in the unit were identified using the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority. Only patients with isolated ventricular septal defects diagnosed in the first year of life were included. Exclusion criteria were 1) children >1 year of age at the time of first encounter, 2) defaulted follow-up before 6 months of life with persistent defect on last encounter or 3) associated with other congenital heart lesions, including but not limited to atrioventricular septal defect, tetralogy of Fallot, transposition of the great arteries, tricuspid atresia, and coarctation of the aorta. Patient with minor associated anomalies, including small patent ductus arteriosus, small secundum atrial septal defect, mild pulmonary stenosis and mild mitral regurgitation were included.

Medical records were reviewed for patients' demographics, clinical data, echocardiogram images and reports. The following data were collected: sex, birth weight, gestational age, ethnicity, comorbid conditions, age at first presentation with signs of VSD, presenting symptoms, size and anatomical type, presence of other congenital heart diseases, presence of complications, presence of heart failure and need for medical or surgical treatment, and time of spontaneous defect closure.

Echocardiography with colour flow mapping was performed in all patients to confirm the diagnosis of VSD. The VSDs were categorised as muscular, perimembranous, or subarterial, according to the classification of Gatzoulis et al.<sup>14</sup> Based on the dimension of defect at the first echocardiogram, the defects were classified as small (<3 mm), medium (3-6 mm), large (>6 mm). Follow-up visits were arranged at intervals of months to one year, depending on clinical need. Referral to a tertiary centre

would be arranged if surgical closure was considered necessary. When the classical heart murmur disappeared, an echocardiogram would be performed. Spontaneous closure of defects was confirmed when the defect could not be identified by 2D echocardiogram and colour flow mapping. The study included follow-up information of the patients up to at least 6 years of age or until spontaneous VSD closure. Patients who defaulted follow-up after 6 months of age, but before documented spontaneous closure of VSD on echocardiography will be analysed as persistent VSD.

## Statistics

Statistical analyses were performed with SPSS version 27 software. Continuous variables were expressed as mean  $\pm$  SD, while categorical variables were expressed as number of cases and percentages. Chi-square test was used for statistical analysis between categorical variables. The rate of events was calculated using Kaplan-Meier curves and compared by the log-rank test. The association of selected variables with the outcome was assessed using Cox's proportional regression model with stepwise multivariable procedures. Hazard ratios (HR) with the corresponding 95% confidence interval (CI) were estimated. A p-value less than 0.05 was regarded as statistically significant.

## Results

There were 40,664 live births in our hospital between 1st January 2004 and 31st December 2014. Isolated VSDs were identified in 247 infants, of whom 202 were born in the hospital. The incidence of isolated VSD was 4.97 per 1000 live births. Ten cases, who were lost to follow-up before 6 months of age (1 day to 5 months) with persistent defect on last encounter, were excluded from further analysis.

Baseline characteristics of the 237 patients undergoing follow-up study were shown in Table 1. Of all patients, 116 (49%) were male. Majority (95%) of them were ethnically Chinese. Thirty-two (14%) infants had birth weights below 2500 grams while 28 (12%) infants were born prematurely before 37 weeks of gestation, including 1 (0.4%) infant born at 27 weeks of gestation. The mean gestation was 38.4 weeks, with a range of 27 weeks to 42 weeks. The mean birth weight was 3005 g, with a range of 735 g to 4514 g.

The infants first presented at a mean age of 10.6 days, ranging from 0 days to 241 days. The most common presenting clinical feature was heart murmur (96%), followed by dysmorphism (2%), and heart failure symptoms (1%). Additionally, 0.8% of cases were detected during antenatal ultrasound.

There were six (3%) cases with chromosomal abnormalities, including three cases of Down syndrome. Three cases had multiple congenital malformations with no genetic diagnosis.

Death occurred in one infant with Down syndrome and medium-sized perimembranous VSD requiring medical treatment, who died on arrival to the hospital at the age of 3 months with concurrent gastroenteritis.

Except for 17 (7%) cases lost to follow-up by 6 years of age, all cases had been follow-up until at least 6 years of age or until VSD closure. Among cases where VSD persisted (56, 24%), the mean follow-up duration was 8.5 years, ranging from 6.3 years to 16 years.

Table 2 compared the characteristics of the 237 VSDs. Perimembranous VSDs were most common (140, 59%), followed by muscular VSDs (82, 35%) and subarterial VSDs (15, 6%). For muscular VSDs, midventricular defects were more common (43, 18%), followed by apical defects (31, 13%) and outlet defects (6, 3%). Most (91%) of cases had a single defect. The mean defect size was 3.11 mm, with a range of 0.5 mm to 9 mm. Majority (66%) of the VSDs were small defects. The 156 small defects included mainly similar proportions of perimembranous (46%) and muscular (50%) VSDs, while only 4% were subarterial. Of 62 medium defects, most (87%) were perimembranous, while only 5% were muscular and 8% were subarterial. The 19 large defects were mostly perimembranous (79%), followed by subarterial (16%) and muscular (5%). There was a statistically significant association between anatomical site and size of VSD ( $p < 0.001$ ). Muscular VSD is associated with small defect while perimembranous and subaortic VSD had higher

proportion of medium and large defect. Co-existing minor cardiac abnormalities on first imaging included patent foramen ovale (101, 43%), small patent ductus arteriosus (28, 12%), small atrial septal defect (16, 7%), mild pulmonary stenosis (2, 0.8%), mitral valve incompetence (3, 1%), and left superior vena cava (2, 0.8%). There was no statistically significant association between presence of co-existing minor cardiac defect and anatomical site ( $p = 0.80$ ) or size ( $p = 0.36$ ) of VSD. Subsequent complications associated with the VSD included right coronary cusp prolapse (8, 3%), aortic incompetence (5, 2%), left ventricle to right atrium shunting (9, 3%), and

**Table 1** Baseline characteristics of the study population

Variable	Number of cases (%) / Mean ± SD
Sex	
Male	116 (49%)
Female	121 (51%)
Ethnicity	
Chinese	225 (95%)
Non-Chinese	12 (5%)
Birth weight (grams)	3005 ± 537
≥2500	205 (86%)
<2500	32 (14%)
Gestational age (weeks)	38.4 ± 2.1
Full-term ≥37	208 (88%)
Preterm <37	28 (12%)
Age at first presentation (days)	10.6 ± 29.0
Co-existing minor cardiac abnormalities	
Patent foramen ovale	101 (43%)
Small patent ductus arteriosus	28 (12%)
Small atrial septal defect	16 (7%)
Mild pulmonary stenosis	2 (0.8%)
Mitral valve incompetence	3 (1%)
Left superior vena cava	2 (0.8%)

**Table 2** Comparison on anatomical type and size of VSDs

	Perimembranous	Muscular	Subarterial	Total
Small	71	78	7	156 (66%)
Medium	54	3	5	62 (16%)
Large	15	1	3	19 (8%)
Total	140 (59%)	82 (35%)	15 (6%)	
$\chi^2$	49.5			
p	<0.001			

double-chambered right ventricle or right ventricular outflow tract obstruction (3, 1%). All cases of right coronary cusp prolapse or aortic incompetence were related to subarterial VSDs while all cases of double-chambered right ventricle or right ventricular outflow tract obstruction were related to perimembranous VSDs.

The disease course according to size and anatomical type was shown in Figure 1. Forty-seven (20%) cases developed heart failure that required medical treatment with a mean duration of 15.6 months. Twenty-one (9%) patients required surgical closure of VSD at a mean age of 17.8 months and a range from 3 months to 64 months. The most common indication for surgery was heart failure despite medical treatment (18 cases, 86%), followed by right coronary cusp prolapse or aortic incompetence (2 cases, 10%) and right ventricular outflow tract obstruction (1 case, 5%). Of all cases that required surgical closure of VSD, 15 (71%) were perimembranous, and 6 (29%) were subarterial. No muscular VSD required surgical closure. Eight (38%) patients had residual defect after surgery, two had pericardial effusion and one developed right ventricular outflow tract obstruction.

Spontaneous closure was observed in 149 patients (63%), of whom 143 (60%) occurred before 6 years of age. Rates of spontaneous closure at the end of 6 months, 1, 2 and 6 years of age were 16%, 30%, 45% and 60% respectively (Figure 2). Kaplan-Meier curves for spontaneous closure showed a significant difference

among perimembranous, muscular and subarterial VSDs ( $P < 0.001$ ) (Figure 2). The highest rates of spontaneous closure were seen in muscular VSDs at 22%, 43%, 65% and 79% respectively at the end of 6 months, one, two and six years of age; while the corresponding rates for perimembranous VSDs were 14%, 26%, 38% and 55% respectively. Only 1 of the 15 subarterial VSDs closed spontaneously, and it occurred at 38 months of age. After 6 years of age, 6 (3%) defects, including 3 muscular and 3 perimembranous, closed spontaneously at the age of 78 to 140 months.

Risk factors for VSD persistence were identified through multivariate analysis and shown in Table 3. Larger defect size, subarterial location, heart failure requiring medical treatment, and male sex were found to be predictive factors for VSDs persistence. Perimembranous or muscular location, in contrast to subarterial, were found to be predictive factors for VSDs closure. Other variables, including number of defects, gestational age, birth weight, presence of genetic mutation or multiple congenital malformations were not found to be a risk factor for VSD persistence.

## Discussion

Isolated VSDs were the most common congenital heart disease in newborns. A local study in 1996 mentioned that

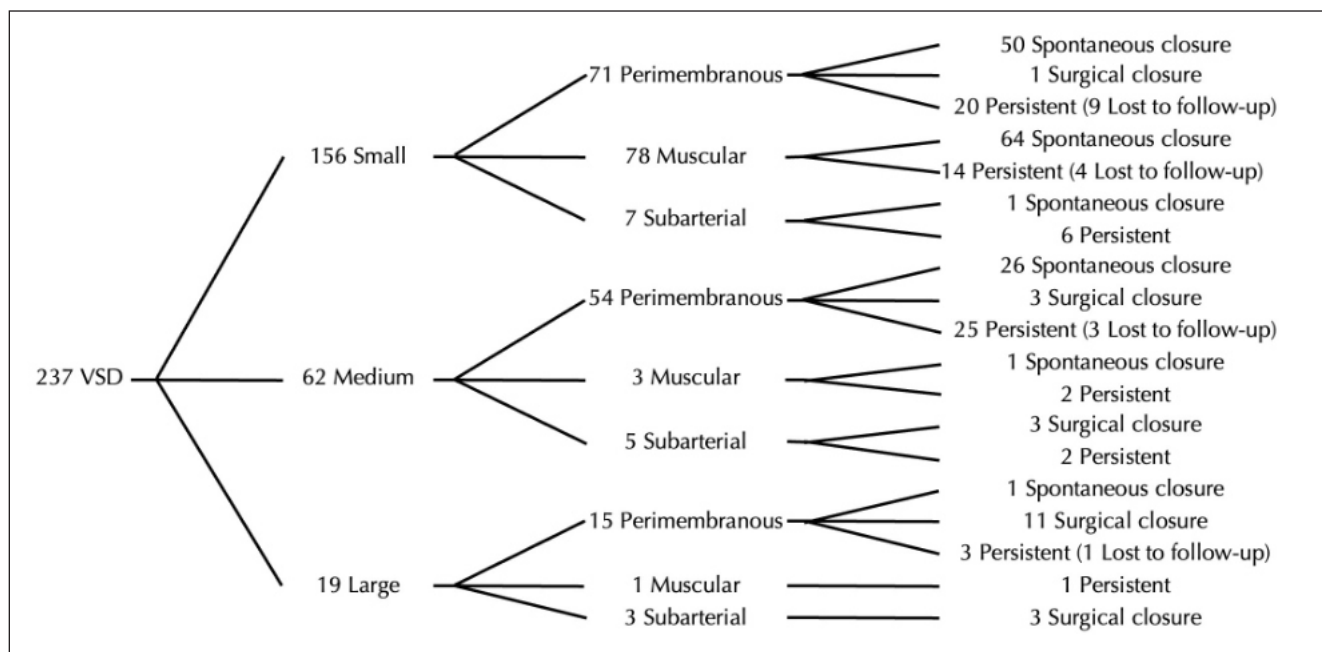


Figure 1. Flow chart of natural history of 237 VSDs.

the incidence of VSD in Hong Kong was comparable to the West, but the exact incidence was not reported.<sup>12</sup> The incidence of VSD in this study was 4.97 per 1000 live births. The present study was a retrospective cohort with a longer follow-up period of at least 6 years. The incidence reported in the previous study was variable, depending on the sample size, age, and screening methods. Our result was similar to the previous studies with retrospective review of medical records on clinically detectable VSDs (from 2.3/1000 to 10.45/1000).<sup>2,4,5</sup> However, compared with the incidence reported from echocardiographic

screening of all newborns (16.7/1000 to 53.2/1000), our study had a lower incidence.<sup>3,6-11</sup> The difference can result from a higher detection rate of clinically asymptomatic, silent, and very small VSDs in echocardiographic screening. It was reported that heart murmur was detected in only 10.7% to 62% of defects.<sup>3,6,8,15</sup> In contrast to our study, 96% of infants presented with a heart murmur. Thus, the true incidence of VSD in the local population is likely to be higher as some silent and asymptomatic VSDs remained undiagnosed and closed spontaneously before detection. However, the findings in our study likely

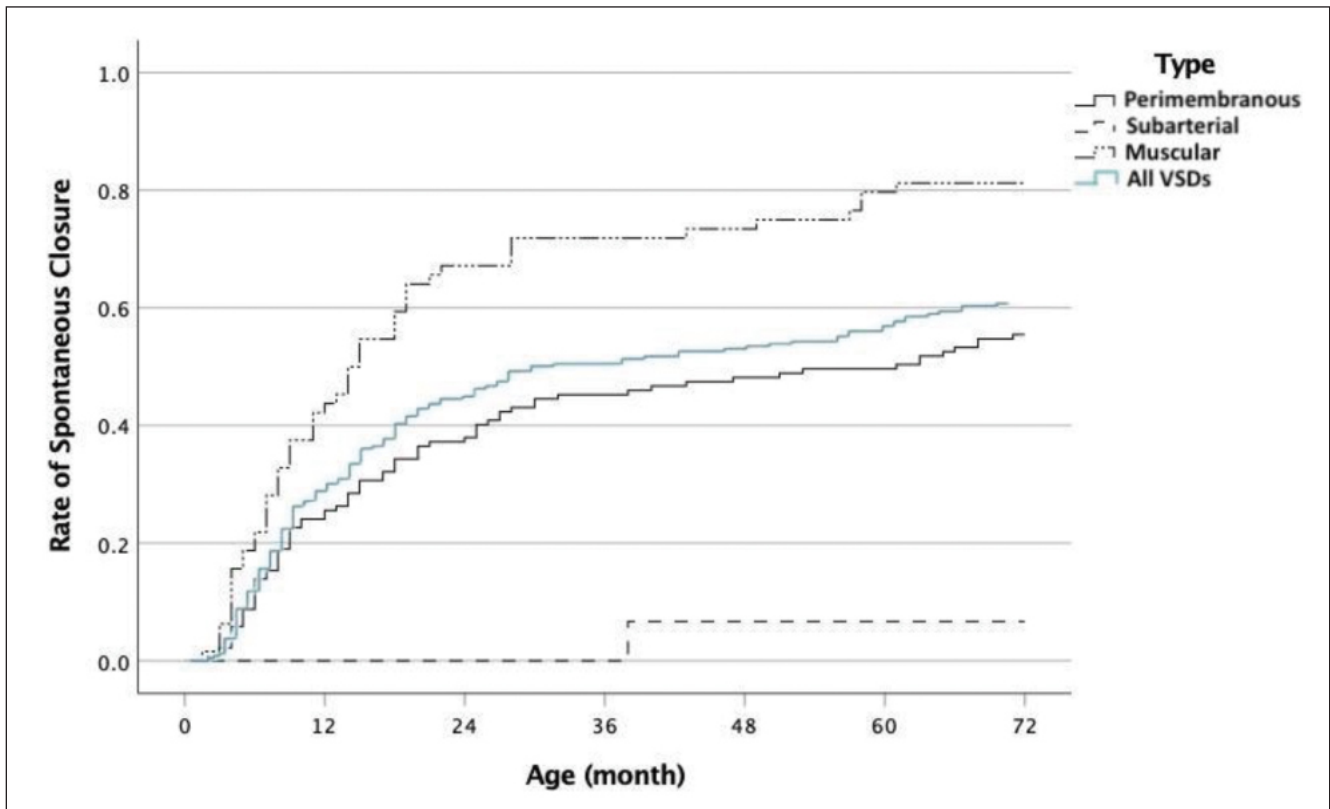


Figure 2. Kaplan-Meier curves for spontaneous closure in perimembranous, muscular, subarterial and all VSDs.

Table 3 Cox multivariate analysis of factor for spontaneous closure in isolated VSDs

Variable	P-value	HR	95% CI
Male vs Female	0.018	0.666	0.475-0.933
Age at first presentation	0.020	0.989	0.979-0.998
Type of defects			
Perimembranous	0.019	2.283	1.148-4.541
Muscular	0.030	2.154	1.079- 4.300
Subarterial	0.018	0.203	0.054-0.760
Defect size	<0.001	0.724	0.607-0.864
Heart failure requiring medical treatment	0.013	0.354	0.156-0.803

represent a reasonable minimum incidence of clinically detectable VSDs according to the usual medical practice.

In this study, the most common VSD location was perimembranous (59%), followed by muscular (35%) and subarterial (6%). Subarterial or subpulmonic VSDs were reported to be more common among Asians. Studies from Asian countries reported 1.3% to 14% of defects were subarterial or subpulmonic VSDs, while studies from the West reported only up to 1.8% (Table 4).<sup>2,5,7,8,16-18</sup> The incidence of subarterial VSDs in our study was comparable with other studies from Asian countries. Subarterial VSDs rarely close spontaneously, and many required surgical closure because of coronary cusp prolapse or aortic regurgitation rather than heart failure. In our study, only 1 out of 15 (7%) subarterial VSDs closed spontaneously, while 6 (40%) required surgery before 6 years old. Findings were comparable to previous studies, which reported spontaneous closure rates of 0-10% for subarterial VSDs (Table 4).<sup>2,7,8,19</sup> However, the surgical closure rate of subarterial defects report varied between studies (0-100%), depending on the duration of study and case selection.<sup>2,7,8,19</sup> The low rate of spontaneous closure of subarterial VSDs could be explained by the unique anatomical features, which in contrast to muscular or perimembranous VSDs, cannot be closed through muscular hypertrophy or tricuspid valve aneurysm formation. Spontaneous closure of subarterial VSDs is usually achieved by prolapse of aortic valve cusp and should be considered as pathological progression instead.<sup>20</sup>

The overall surgical closure rate of 9% was low compared to studies performed in referral centres with reported rates from 20-26%, likely because of a higher proportion of haemodynamically significant defects.<sup>19,21,22</sup> On the other hand, studies with VSD diagnosed through echocardiographic screening of newborns reported lower surgical closure rates of 1.9% and 9.3%.<sup>6,9</sup> However, in the study by Zhao et al which also employed newborn screening, the intervention rate was as high as 16%,

explained by the more widespread use of transcatheter closure of perimembranous VSD in China.<sup>7</sup> In our study, none of the muscular VSDs required surgical closure, as 93% were small defects. On the other hand, the size of perimembranous VSDs varies, 11% were classified as large, and 10% required surgical closure eventually.

In the present study, spontaneous closure of VSD occurred more often within the first 2 years of life (45%) and reached 60% by 6 years of age, and became less likely thereafter. Muscular VSDs (79%) close more frequently and earlier than perimembranous VSDs (55%), while most subarterial VSDs did not close. Comparing with several studies with similar methodology and follow-up durations of 5-6 years, the spontaneous closure rate of perimembranous VSDs was similar to the reported 57% in the more recent study on the Chinese population but higher than the 20% and 28% reported in two earlier studies on the European population.<sup>4,13,23</sup> Possible predilection on race cannot be excluded though more evidence would be necessary. On the other hand, the closure rate of muscular VSDs is similar to the reported 64-69% in the three studies.<sup>4,13,23</sup> In the study employing echocardiographic screening of newborns with a longer duration of follow-up, the high rates of spontaneous closure of muscular VSDs (72.2% at 1 year of age and 97.2% at 7 years of age) may be explained by the inclusion of clinically silent cases as majority.<sup>7</sup> The spontaneous closure rate of perimembranous VSDs for that study was similar (34.3% at 1 year of age and 51.4% at 7 years of age).<sup>7</sup> Other studies with echocardiographic screening performed on all newborns also reported a higher rate of spontaneous closure of muscular VSDs, ranging from 71.4% to 83%, with a follow-up period of 10 months to 1 year.<sup>3,8,11,15</sup> The differences in the findings suggested that the clinically silent VSDs detected by echocardiographic screening had a high chance of spontaneous closure.

In this study, factors including sex, age at diagnosis, type of defect, defect size were found to be related to

**Table 4** Comparison of outcome of studies from region

Study	Position (%)			Spontaneous closure (%)			Follow-up duration (months) (Mean /Absolute)
	Perimembranous	Muscular	Subarterial	Perimembranous	Muscular	Subarterial	
Miyake T et al (Japan) <sup>16</sup>	70	16	14	47	83	10	83
Zhao Q et al (China) <sup>7</sup>	30.9	63.7	5.3	51.4	97.2	0	84
Lin MH et al (Taiwan) <sup>8</sup>	34	65	1	24	83	0	12
Cresti A et al (Italy) <sup>5</sup>	11.3	73.8	0.8	81.8	95	0	72
Turner SW et al (UK) <sup>23</sup>	36.9	62.1	<0.1	29	68	0	65

spontaneous closure of VSD. Such findings were consistent with those reported in previous studies. Cresti et al reported that perimembranous location, multiple defects, and male gender were associated with defect persistence.<sup>5</sup> Turner et al reported defect size, morphology and young age of diagnosis were associated with spontaneous closure.<sup>2</sup> Xu et al found that VSD location was independent predictors of spontaneous closure.<sup>17</sup> Li et al found that defect size was a representative factor of spontaneous closure.<sup>13</sup> Zhao et al reported perimembranous site and defects larger than 4 mm were risk factors for VSD that do not close spontaneously.<sup>7</sup>

## Limitation

The incidence of VSD from this study should be only a minimum incidence that did not include patients born in the hospital but diagnosed elsewhere and did not return at all. A fraction of the deliveries came from visitors from Mainland China who had a short postnatal stay, thus limiting time for diagnosis and follow-up. As a result, 7% of cases were lost to follow-up by 6 years of age. This loss may have led to an underestimation of the true rate of spontaneous closure, as VSDs in participants lost to follow-up were classified as persistent in this study. Secondly, this study was a single-centre retrospective study with a relatively small sample size. Therefore, statistical bias cannot be easily avoided. Finally, the mean follow-up duration of the patients whose VSD remained patent was 8.5 years. Previous studies had shown that VSDs closed spontaneously during adolescence.<sup>2</sup> Therefore, we expect the rate of spontaneous closure would increase on long-term follow-up.

## Conclusion

This study provided updated local information on the incidence, anatomical type, natural history, and spontaneous closure rate of ventricular septal defects diagnosed in infancy in a secondary paediatric service setting in Hong Kong. The incidence of clinically detectable VSD was at least 4.97 per 1000 live births. Perimembranous VSD was the most common type of VSD, followed by muscular VSD. After six years of life, 60% of the VSDs closed spontaneously, mainly occurring in muscular and perimembranous VSDs and rarely in subarterial VSDs.

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## Ethical Approval

This study was approved by Hong Kong East Cluster Research Ethics Committee (Ref. No. HKECREC-2020-049). The requirement for patient consent was waived by the ethics board.

## Declaration

The author has no conflicts of interest to disclose. The author had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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