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年幼兒童經心導管關閉膜邊型心室中膈缺損後長期後遺症的風險因素

Risk Factors of Long-term Sequelae after Transcatheter Closure of Perimembranous Ventricular Septal Defect in Young Children

秦家翊

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中文摘要

背景：

罹患膜邊型心室中膈缺損（pmVSD）的病人，在接受經心導管關閉術而引起的併發症，如殘餘分流和主動脈逆流（AR），近年已陸續有許多研究觀察到。然而，目前尚不清楚與之相關的風險因素，特別是在兒童族群。本研究目的在於尋找 2 至 12 歲的年幼兒童之 pmVSD 經心導管關閉後殘餘分流和 AR 的相關風險因素。

方法和結果：

我們分析了在台大兒童醫院小兒心臟科，於 2011 年至 2018 年間接受經心導管關閉術的 63 名 pmVSD 兒童，其肺循環至全身循環血流比率低於 2.0 的醫療記錄，並進行了至少 3 年的追蹤。所有接受經心導管關閉術治療的兒童的成功率為 98.4%，並無主要嚴重的併發症產生，例如緊急外科手術、永久性高度房室傳導阻滯或死亡。在殘餘分流的部分，心室中膈缺損若大於 4.5mm 則具有顯著較高的持續性殘餘分流風險（勝算比：6.85，p = 0.03）。使用比缺損直徑大 1.5mm 的關閉器尺寸顯示出減少殘餘分流的趨勢（勝算比：0.23，p = 0.06）。而年齡小於 4 歲（勝算比：27.38，95%CI：2.33 – 321.68）和出口型 pmVSD（勝算比：11.94，95%CI：1.10 – 129.81）是關閉 pmVSD 後 AR 惡化的獨立風險因素。

結論：

對於超過 4.5mm 的 pmVSD，需要特別注意追蹤經心導管關閉後的持續性殘餘分流。在考慮 pmVSD 關閉的好處時，仔細評估 AR 風險，特別是對於 4 歲以下兒童以及 pmVSD 分類，是至關重要的。

關鍵詞: 心室中膈缺損、經心導管關閉術、年幼兒童、殘餘分流、主動脈逆流

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英文摘要

Abstract

Background

Complications arising from transcatheter closure of perimembranous ventricular septal defects (pmVSD) in children, such as residual shunts and aortic regurgitations (AR), have been observed. However, understanding the associated risk factors remains unclear. This study aims to identify risk factors linked with residual shunts and AR following transcatheter closure of pmVSD in children aged 2–12 years.

Methods and Results

Medical records of 63 children with pmVSD and a pulmonary-to-systemic blood flow ratio below 2.0 who underwent transcatheter closure between 2011 and 2018 in National Taiwan University Children Hospital were analyzed with a minimum 3-year follow-up. The success rate of transcatheter closure was 98.4%, with no emergent surgery, permanent high-degree atrioventricular block, or mortality. Defects exceeding 4.5 mm in diameter had significantly higher odds of persistent residual shunt (OR: 6.85, $p = 0.03$). The use of an oversize device (>1.5 mm) showed a trend toward reducing residual shunts (OR: 0.23, $p = 0.06$). Age under 4 years (OR: 27.38, 95% CI: 2.33–321.68) and perimembranous outlet type VSD (OR: 11.94, 95% CI: 1.10–129.81) were independent risk factors for AR progression post-closure.

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Conclusion

Careful attention is crucial for pmVSDs larger than 4.5 mm to prevent persistent residual shunts in transcatheter closure. Assessing AR risk, particularly in children under 4 years old, is essential while considering the benefits of pmVSD closure.

Key Words: Ventricular septal defect; Transcatheter closure; Young children; Residual shunt; Aortic regurgitation

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英文縮寫對照表 Abbreviation List

縮寫	英文全名
ADO	Amplatzer™ Duct Occluder
ADO II	Amplatzer™ Duct Occluder II
AR	Aortic regurgitation
AUC	Area under curve
AV block	Atrioventricular block
BSA	Body surface area
cAVB	Complete atrioventricular block
CI	Confidence interval
CT ratio	Cardiothoracic ratio
HR	Hazard ratio
IQR	Interquartile range
LVEDD	Left ventricular end-diastolic diameter
mPAP	Mean pulmonary arterial pressure
NYHA	New York Heart Association classification
OR	Odds ratio
PmVSD	Perimembranous ventricular septal defect

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PO	Perimembranous outlet
PT	Perimembranous trabecular
Qp/Qs	Pulmonary-to-systemic blood flow ratio
RBBB	Right bundle branch block
RCC	Right coronary cusp
ROC	Receiver operating characteristic
SD	Standard deviation
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VSD	Ventricular septal defect
VT	Ventricular tachycardia

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Introduction

Epidemiology of Ventricular Septal Defect

Ventricular septal defect (VSD) is the most common congenital heart disease in children. According to a nationwide cohort study in Taiwan (refer to Supplement 1), the prevalence of congenital heart disease is approximately 13.1 per 1,000 live births, with VSD accounting for 4 per 1,000 live births[1]. Perimembranous VSD (pmVSD) can be closed spontaneously by aneurysmal transformation of the tricuspid valve[2]. However, the progression of VSD-related conditions is contingent upon size and duration. While large VSDs can lead to congestive heart failure during childhood and pulmonary hypertension in adulthood, unrepaired small pmVSDs may still manifest complications such as endocarditis, aortic regurgitation (AR), and arrhythmias in adulthood[3].

Small VSDs are defined as having normal pulmonary artery pressure, shunting from the defect less than 50%, pulmonary-to-systemic blood flow ratio (Qp/Qs) less than 2, absence of VSD-related AR, and absence of heart failure symptoms. A prospective study tracking 118 children with small VSDs demonstrated an 8-year event-free survival rate of 95.5±1.9% (with events defined as death, endocarditis, or VSD surgery)[4]. Consequently, the management of small pmVSDs in childhood remains subject to debate.

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Managing Perimembranous Ventricular Septal Defects: Treatment Options and Related Complications

For persistent pmVSD, transcatheter closure may be applied as an alternative to surgical repair. Transcatheter closure of VSD was first described in late 1980s[5]. Previous studies have reported a high success rate of up to 98% for transcatheter VSD closure[6, 7]. A meta-analysis[8] comparing surgical repair versus transcatheter closure of VSD revealed similar success rates, overall complications, and rates of complete atrioventricular block, but lower rates of residual shunts and need for blood transfusions (Supplement 2). However, specific minor complications[9], such as AR and residual shunts, persisted and should not be ignored.

Carminati et al. documented that age and weight demonstrated associations with early complications, such as mortality, vascular complications, hemolysis attributed to residual shunts, infections, device embolization, and arrhythmias, following transcatheter closure of pmVSD[10]. Shrestha M. et al. demonstrated usage of PFM coil was borderline ($p = 0.14$) associated with development of AR within one year after the transcatheter pmVSD closure[11].

In previous experiences of National Taiwan University Children Hospital[12], the success rate of transcatheter closure of pmVSDs was reported as 95.2%. The incidence

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of residual shunts after closure was 5.9% after 1 year and 4.5% after 2 years. Importantly, no cases of complete atrioventricular block were reported.

However, there is limited discussion on the risk factors associated with the development of residual shunts and the onset of new-onset AR within three years following transcatheter closure of pmVSD in young children who underwent such interventions. Additionally, the safety and efficacy in this patient group are not well known. Therefore, this retrospective study, conducted at a tertiary medical center, was aimed to identify and clarify these factors.

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Methods

Patients

We retrospectively reviewed the medical records of 63 children aged 2–12 years with pmVSD whose Qp/Qs was below 2.0 and had received transcatheter closure in National Taiwan University Children's Hospital between August 2011 and February 2018.

The indications for transcatheter closure in these patients included: (1) heart failure symptoms, including failure to thrive, (2) cardiothoracic ratio more than 0.5 in chest plain film, (3) the z-score of M-mode left ventricular end-diastolic diameter (LVEDD) more than 2, (4) prolapse of the coronary cusp with or without AR in transthoracic echocardiography (TTE), and (5) Qp/Qs more than 1.5.

The perimembranous inlet type VSD was excluded from transcatheter closure due to concerns about the proximity of the conduction system along the posterior-inferior rim, which may raise the risk of heart block, as reported by Yip et al[13]. We analyzed patients' baseline characteristics, cardiac catheterization–related hemodynamic data, transcatheter closure complications, and echocardiography before and after (during follow-up) the intervention. The z-score of M-mode LVEDD was calculated according to the Boston Children's Hospital z-score system. Severity of residual shunt after

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pmVSD closure was classified into trivial, mild, moderate, and severe (<1, 1–2, 2–4, and ≥4 mm color jet width, respectively)[10]. To assess the degree of AR, we measured the proximal jet width from the long-axis views and its ratio to the left ventricular outflow tract diameter (mild: <25%, moderate: 25%–64%, severe: ≥65%) and the width of vena contracta (mild: <0.3 cm, moderate: 0.3–0.6 cm, severe: ≥0.6 cm)[14]. AR progression was defined as the increase in AR severity after the pmVSD closure.

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Cardiac catheterization protocol

Hemodynamic data were assessed before the intervention, and the Qp/Qs ratio was calculated according to Fick's principle. We selected Amplatzer™ Duct Occluder (ADO) and Amplatzer™ Duct Occluder II (ADO II) (Abbott Structural Heart; Plymouth, MN, USA) or HeartR pmVSD Occluder (Lifetech Scientific, Shenzhen, China) based on both angiography and transesophageal echocardiography (TEE). We crossed the defect retrograde, snaring and establishing an arteriovenous rail through the pmVSD according to a procedure detailed elsewhere[12] and an antegrade approach was utilized to implant all ADO, ADO II and HeartR pmVSD Occluder. We conducted TEE and left ventriculogram to check the residual shunt and cardiac valvular function. The device was released under TEE and fluoroscope guidance. Left ventriculogram, aortogram, and TEE were also employed to evaluate the adequacy of device position, residual shunt, and AR after device implantation. Furthermore, oral aspirin was administered (3–5 mg/kg/day) for 6 months after discharge.

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TTE follow-up

Echocardiographic follow-up for possible complications after transcatheter closure of pmVSD[15] was arranged at 0–3 months, 3–6 months, 6–12 months, 1 year after discharge, and every 6–12 months thereafter. The device position, residual shunts, LVEDD, and cardiac valvular function such as AR were documented. Follow-up data were collected until September 2021. We also calculated patient survival after the date of transcatheter closure of pmVSD.

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Statistical analysis

Categorical variables were analyzed using chi-square test, represented by percentage. For the continuous variables, Student's *t*-test, paired *t*-test, or Mann–Whitney *U* test was used, represented by mean (SD) or median (interquartile range). The following independent variables were included in the analysis: age at intervention, weight percentile at procedure, sex, defect type (perimembranous trabecular [PT] or perimembranous outlet [PO]), presence of aneurysmal transformation, defect diameter (TTE or TEE), LVEDD z-score, Qp/Qs, device type (ADO, ADO II, or HeartR), device diameter, and difference in device diameter and defect diameter measured by TEE. The risk factors for residual shunts and AR progression were analyzed using multiple logistic regression. Independent variables with a *p*-value below 0.2 in the univariate analysis were included in the receiver operating characteristic (ROC) analysis and multivariate model (odds ratios (OR) and 95% confidence intervals (CIs) were calculated). The duration of follow-up covered the time from day 1 after the transcatheter closure to the last echocardiography of the patients. The probability of persistent residual shunt and AR progression-free survival was estimated using the Kaplan–Meier method; the log-rank test was used for univariate comparison. The persistent residual shunt and AR progression-free survival after pmVSD closure were evaluated using Cox proportional-hazards regression. All analyses were conducted

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using SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA). Two-tailed $P<0.05$ was considered statistically significant.

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Results

General characteristics and interventional data

A total of 63 patients with pmVSD underwent transcatheter closure, of which 34 (54.0%) were male. Table 1 summarizes their basic demographic and hemodynamic data. The median age was 6.8 (5.1–9.0) years, and the median weight was 22.4 (16.6–29.0) kg. Among them, fifty had PT type VSD and 13 had PO type VSD. The median diameter of the pmVSD measured in 59 patients was 3.5 (2.9–4.6) mm measured by TTE within 4 months before catheterization. The median LVEDD measured in 61 patients was 3.9 (3.6–4.3) cm, and its median z-score was +0.9 (-0.3– +1.9). Patients with Qp/Qs above 1.3 had significantly higher LVEDD z-scores than those with below 1.3. (1.48 ± 1.67 vs. 0.47 ± 1.24, $p = 0.009$). Aneurysmal transformation was detected in 59 patients through methods such as TTE, TEE or left ventricular angiography. AR was found in 17 patients. In addition, 19 patients (30.2%) had associated cardiac abnormalities including mild right ventricular outflow tract obstruction ($n = 4$), patent ductus arteriosus status after transcatheter closure ($n = 3$), subaortic ridge without LV outflow tract obstruction ($n = 2$) or with mild LV outflow tract obstruction ($n = 2$), patent foramen ovale ($n = 2$), atrial septal defect ($n = 2$), mitral valve prolapse ($n = 2$), LV noncompaction ($n = 1$), small coronary arteriovenous fistula ($n = 1$), and persistent left superior vena cava ($n = 1$).

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Table 1. Baseline Characteristics

Characteristic	Values
Age (year)	6.8 (5.1 to 9.0)
Male	34 (54.0)
Height (cm)	119.0 (106.0 to 135.0)
Weight (kg)	22.4 (16.6 to 29.0)
Weight percentile	49.4 (22.6 to 73.0)
BSA (m^2)	0.9 (0.7 to 1.0)
NYHA	
I	53 (84.1)
II	9 (14.3)
III	1 (1.6)
Pre-catheterization echocardiography	
PO type of VSD	13 (20.6)
Defect diameter by TTE (mm)	3.5 (2.9 to 4.6)
LVEDD (cm)	3.9 (3.6 to 4.3)
Total (z-score)	0.9 (−0.3 to 2.0)
Qp/Qs ≥ 1.3 (z-score)	1.3 (0.2 to 2.8)
Qp/Qs < 1.3 (z-score)	0.4 (−0.4 to 1.4)
Defect diameter by TEE (mm)	4.0 (3.5 to 5.0)
Aneurysmal transformation	59 (93.7)
Hemodynamic data	
Qp/Qs	1.3 (1.1 to 1.5)
mPAP (mmHg)	17.0 (14.0 to 20.0)
Indications for VSD closure	
Symptoms or signs of heart failure	12 (19.0)
Failure to thrive	6 (9.5)
CT ratio ≥ 0.5	42 (66.7)
LVEDD z-score ≥ 2.0	14 (22.2)
RCC prolapse	42 (66.7)
Aortic regurgitation	17 (27.0)
Qp/Qs ≥ 1.5	16 (25.4)

Values are numbers (%) and median (interquartile range). BSA, body surface area; NYHA, New York Heart Association classification; PO, perimembranous outlet; TTE, transthoracic echocardiography; LVEDD, left ventricular end-diastolic diameter; TEE, transesophageal echocardiography; Qp/Qs, pulmonary-to-systemic blood flow ratio; mPAP, mean pulmonary arterial pressure; CT ratio, cardiothoracic ratio; RCC, right coronary cusp.

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Regarding the hemodynamic data of catheterization, the median Qp/Qs was 1.3 (1.1–1.5). The median mean pulmonary arterial pressure (mPAP) was 17.0 (14.0–20.0) mmHg, and more than 25 mmHg obtained in five patients. The median defect diameter measured by TEE was 4.0 (3.5–5.0) mm. The median difference in defect diameter measured by TEE and TTE was 0.6 mm (IQR: -0.4–1.5 mm). Furthermore, the indication of pmVSD closure in the current cohort were listed in Table 1 and 42 patients had 2 or more indications.

Device implantation for pmVSD closure was successful in 62 (98.4%) patients. ADO and ADO II were properly deployed in 23 and 24 patients, respectively. Additionally, 15 patients were implanted with HeartR pmVSD occluder. We failed to conduct transcatheter closure on only one 3-year-old female because she developed significant AR and residual shunts after we deployed a 4 mm ADO II device.

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Early complications

One female aged 4 years 10 months experienced device (ADO 8/6 mm) dislodgement during the procedure. Nonetheless, we successfully retrieved it and deployed a new 8mm ADO device (9-PDA-006).

No atrioventricular block was detected during or 1 day after the procedure. Other early events within one day after pmVSD closure (Table 2) were the onset of transient arrhythmic or conductive events (n = 13), anesthesia-related complications such as nausea or vomiting (n = 5), and fever (n = 2). Those who had fever received empirical intravenous antibiotics until it subsided. The median duration of staying in the intensive care unit was one day, and the median hospitalization duration was three days.

Table 2. Early Complications after PmVSD Closure.

Complications	*N* (%)
Device dislodgement	1 (1.6)
Arrhythmic events	
Short-run VT	2 (3.2)
AV block	0 (0)
Transient junctional rhythm	1 (1.6)
Complete RBBB	1 (1.6)
Incomplete RBBB	9 (14.3)
Residual shunt	27 (43.5)
New aortic regurgitation	21 (45.7)
Fever	2 (3.2)
Nausea/vomiting	5 (7.9)

PmVSD, perimembranous ventricular septal defect; VT, ventricular tachycardia; AV, atrioventricular; RBBB, right bundle branch block.

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Post-intervention follow-up

The median follow-up time after discharge in 62 patients was 46.1 (36.8–62.3) months. However, four of them were lost to follow-up after 1 year. Moreover, five patients had persistent conduction problems after intervention for 1 year (1 had right bundle branch block [RBBB], and 4 had incomplete RBBB). None of the patients experienced complete atrioventricular block (cAVB) during the follow-up period.

Residual shunts

Since day 1 after the pmVSD closure, 27 (43.5%) patients had trivial or small residual shunts. The median follow-up time was 47.9 (37.3–65.0) months. The probability of persistent residual shunt of 27 patients at 1, 6, and 12 months after transcatheter closure was 81.5%, 50%, and 44.4%, respectively. We also found that 9 (14.5%) patients had trivial or small residual shunts for more than 3 years after pmVSD closure. Hence, univariate analysis was conducted to explore the potential risk factors of persistent residual shunts longer than 3 years (Table 3). Results showed that the median diameter of pmVSD (on TEE) in those with residual shunts after procedure was 5.5 mm, which was significantly larger than that of those without (4 mm, $p = 0.002$). The defect diameters of the patients with residual shunts were all larger than 4.5 mm. However, of the 53 patients without residual shunt, only 18 (34.6%) had a VSD larger than 4.5 mm

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($p < 0.001$). The median difference between the diameter of the device and the diameter of pmVSD on TEE was 2.0 (1.0 to 3.0) mm larger in patients without residual shunts and 1.0 (0.5 to 2.5) mm larger in those with residual shunts. When the difference exceeding 1.5 mm, the number of patients was 33 (63.5%) versus 3 (33.3%, $p = 0.142$).

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Table 3. Persistent Residual Shunts 3 Years after PmVSD Closure.

Variable	No residual shunt (*n* = 53)	Residual shunt (*n* = 9)	*P* value
Age (year)*	6.8 (5.2 to 9.2)	6.5 (5.2 to 9.7)	0.7
Male	30 (56.6)	4 (44.4)	0.719
Weight percentile*	49.0 (22.6 to 72.7)	53.9 (39.0 to 80.9)	0.337
PO type of VSD	10 (18.9)	2 (22.2)	1
RCC prolapse	35 (66.0)	6 (66.7)	1
Aneurysmal transformation	49 (94.2)	8 (88.9)	0.481
LVEDD z-score*	0.8 (−0.4 to 2.0)	1.2 (0.4 to 2.0)	0.425
Qp/Qs*	1.3 (1.1 to 1.5)	1.4 (1.2 to 1.6)	0.498
VSD diameter on TTE (mm)*	3.5 (2.9 to 4.6)	3.4 (3.0 to 5.1)	0.765
VSD diameter on TEE (mm)*	4.0 (3.3 to 5.0)	5.5 (5.0 to 6.0)	0.002
Diameter ≥ 3.5 mm	37 (71.2)	9 (100)	0.097
Diameter ≥ 4.0 mm	29 (55.8)	9 (100)	0.011
Diameter ≥ 4.5 mm	18 (34.6)	9 (100)	<0.001
Diameter ≥ 5.0 mm	14 (26.9)	7 (77.8)	0.006
Device type			0.610
ADO	19 (35.8)	4 (44.4)	
ADO II	20 (37.7)	4 (44.4)	
HeartR	14 (26.4)	1 (11.1)	
Device diameter minus VSD diameter on TEE (mm)			
Difference (mm)*	2.0 (1.0 to 3.0)	1.0 (0.5 to 2.5)	0.241
Difference ≥ 0.5	45 (86.5)	7 (77.8)	0.609
Difference ≥ 1.0	42 (80.8)	6 (66.7)	0.386
Difference ≥ 1.5	33 (63.5)	3 (33.3)	0.142
Difference ≥ 2.0	28 (53.8)	3 (33.3)	0.301

Values are numbers (%), median (interquartile range). * Mann–Whitney U test. ADO, Amplatzer Duct Occluder; ADO II, Amplatzer Duct Occluder II; HeartR, HeartR pmVSD Occluder; PO, perimembranous outlet; VSD, ventricular septal defect; RCC, right coronary cusp; LVEDD, left ventricular end-diastolic diameter; Qp/Qs, pulmonary-to-systemic blood flow ratio; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

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The ROC analysis also demonstrated an area under curve (AUC) of 0.82 (95% CI: 0.72 to 0.93) with a cutoff point 4.52 mm in VSD diameter on TEE and the AUC of 0.62 with the cutoff point 1.48 mm in the difference between diameter of the device and the diameter of pmVSD on TEE, as detailed in Table 4.

Table 4.

ROC Curve Analysis for Risk factors of Residual Shunts.

Variable	No residual shunt	Residual shunt	*P* value	AUC	Cutoff point	Sensitivity	1-Specificity
VSD diameter on TEE (mm)	4.0 (3.3 to 5.0)	5.5 (5.0 to 6.0)	0.002	0.82 (0.72 to 0.93)	4.52	1.00	0.29
Difference of device diameter minus VSD diameter on TEE (mm)	2.0 (1.0 to 3.0)	1.0 (0.5 to 2.5)	0.241	0.62 (0.43 to 0.82)	1.48	0.67	0.37

Values are median (interquartile range), AUC: area under the ROC curve, CI: confidence interval, VSD: ventricular septal defect, TEE: transesophageal echocardiography

Multivariate logistic regression analysis showed that the only independent risk factor of residual shunt lasting for 3 years after the procedure was the diameter of pmVSD above 4.5 mm on TEE (OR: 6.85, 95% CI: 1.28–36.71 [$p = 0.025$]). The diameter of the device minus the diameter of pmVSD on TEE exceeding 1.5 mm, while

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lacking statistical significance, may suggest a potential trend toward reducing residual shunt (OR: 0.23, 95% CI: 0.05–1.08, [$p = 0.062$]).

Taking the time factor into consideration, the survival probability of persistent residual shunt was also higher in patients with pmVSD diameter greater than 4.5 mm than in those without (log-rank test, $p < 0.001$) (Figure 1A). The survival probability of persistent residual shunt significantly reduced for those whose oversize diameter (defined as device diameter minus the measured diameter by TEE) exceeded 1.5 mm (p of log-rank test: 0.042) (Figure 1B), compared to those without.

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Figure 1A. The Survival Probabilities of Persistent Residual Shunt – Stratified by VSD Diameter Greater than 4.5 mm.

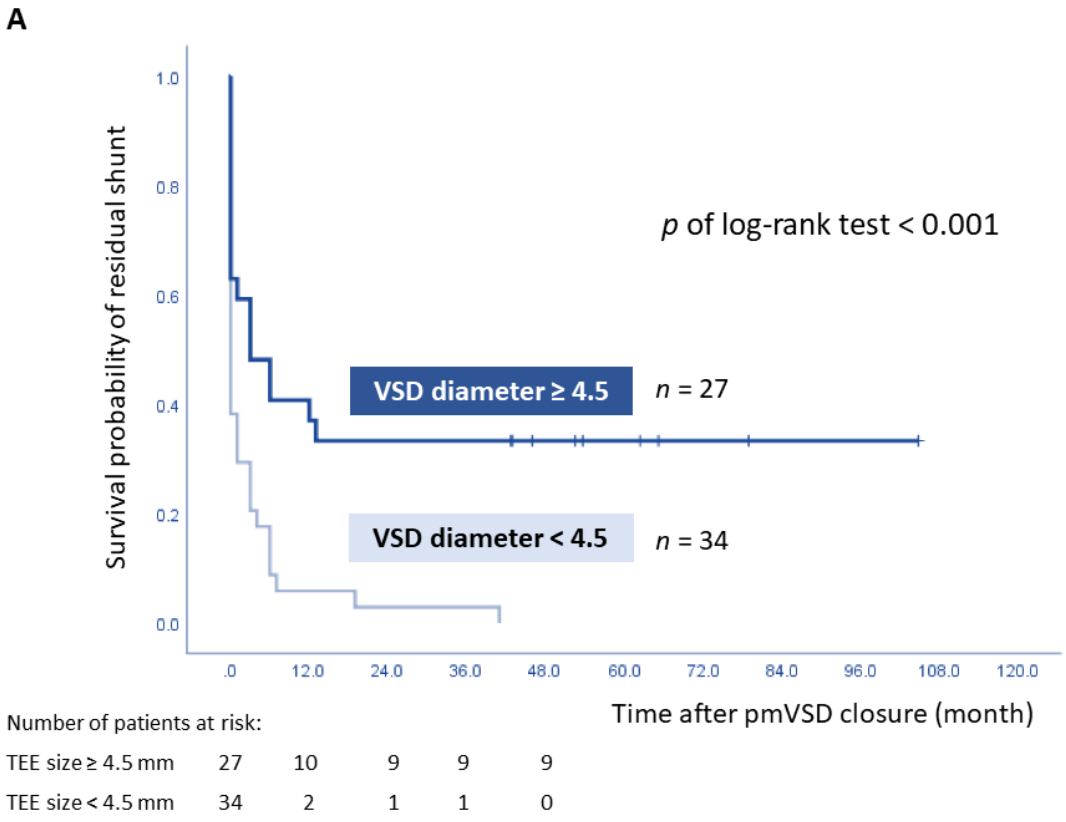

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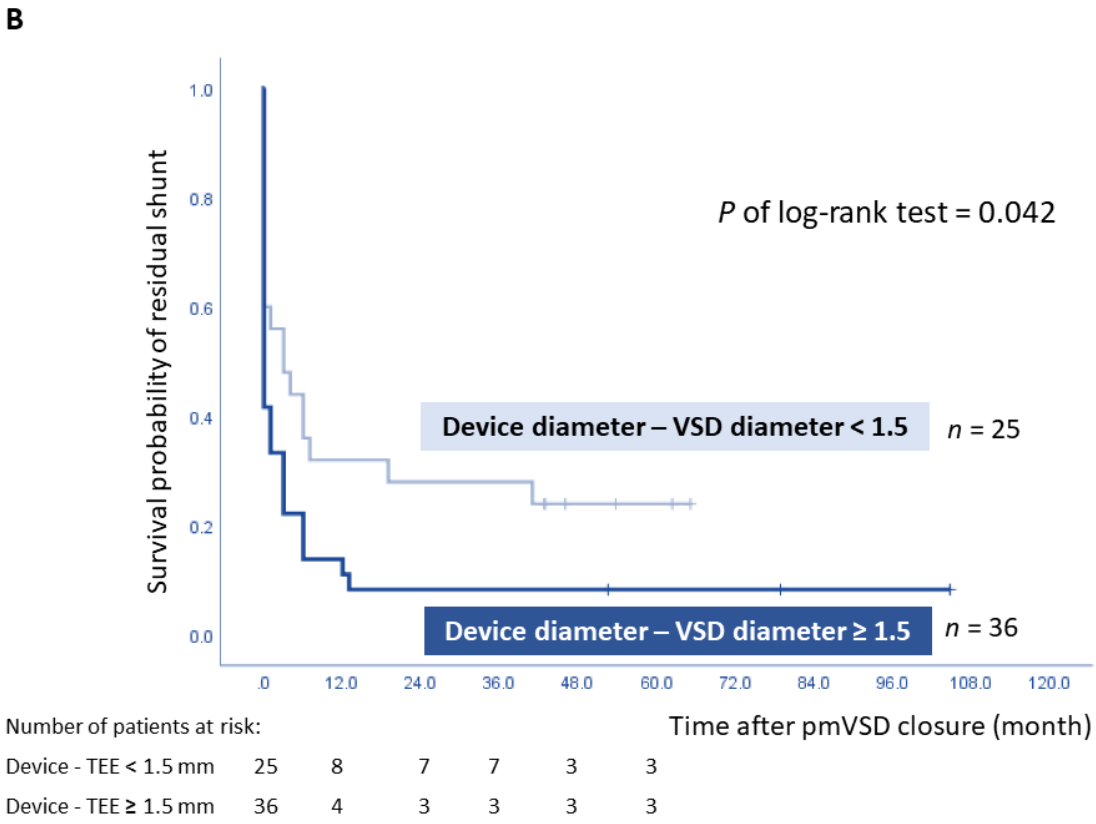
Figure 1B. The Survival Probabilities of Persistent Residual Shunt – Stratified by Oversize Diameter Exceeded 1.5 mm



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To avoid interactions among the potential risk factors, we conducted Cox regression to identify the independent risk factors of persistent residual shunt after transcatheter VSD closure. We found that the VSD diameter (≥4.5 mm) by TEE was the only independent risk factor of persistent residual shunt 3 years after transcatheter VSD closure (hazard ratio [HR]: 0.49, 95% CI: 0.04–0.70, $p = 0.038$). The diameter of the device minus the diameter of pmVSD on TEE greater than 1.5 mm obtained an OR of 1.78 (95% CI: 0.73–4.33, $p = 0.203$); analysis on the remaining variables showed no significance (Table 5).

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Table 5. Cox Proportional-hazards Model of Disappearing Residual Shunt

Variable	HR	95% CI of HR	*P* value
Age (per year)	0.97	0.85 to 1.09	0.587
Male	1.28	0.68 to 2.41	0.451
Weight percentile	0.99	0.98 to 1.01	0.252
PO type VSD	1.13	0.46 to 2.79	0.789
LVEDD z-score	0.95	0.75 to 1.19	0.633
Qp/Qs	0.76	0.16 to 3.56	0.730
VSD diameter on TEE ≥ 4.5 mm	0.49	0.04 to 0.70	0.038
Device diameter minus VSD diameter on TEE ≥ 1.5 mm	1.78	0.73 to 4.33	0.203
Device type			0.299
ADO vs. HeartR	0.57	0.26 to 1.27	
ADO II vs. HeartR	0.58	0.24 to 1.42	

HR: hazard ratio, CI: confidence interval, PO: perimembranous outlet, VSD: ventricular septal defect, LVEDD: left ventricular end-diastolic diameter, Qp/Qs: pulmonary-to-systemic blood flow ratio, TEE: transesophageal echocardiography, ADO: Amplatzer Duct Occluder, ADO II: Amplatzer Duct Occluder II, HeartR: HeartR pmVSD Occluder

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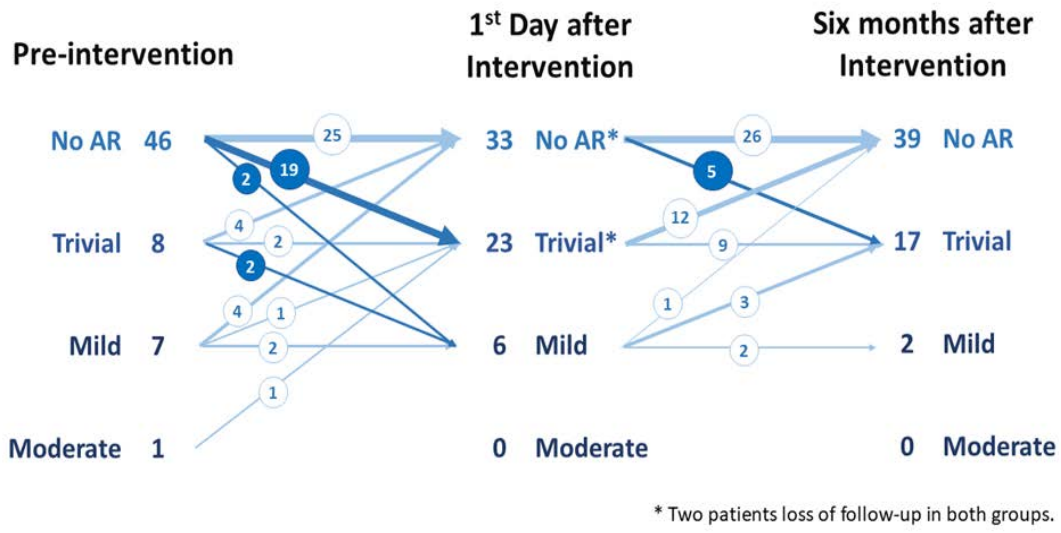
Aortic Regurgitation

New onset or progression of AR severity was observed in 23 patients (37.1%) just 1 day after the procedure (Figure 2). Among the 8 patients who had mild or more severe AR prior to their transcatheter closure of VSD, no further progression in AR severity was detected. Within the cohort, 21 patients exhibited new-onset trivial or mild AR, while 2 patients showed a progression from trivial to mild AR. The condition persisted in 5 patients six months after the procedure (Figure 2).

Figure 2. The Evolution of Aortic Regurgitation (AR) Following the Intervention.



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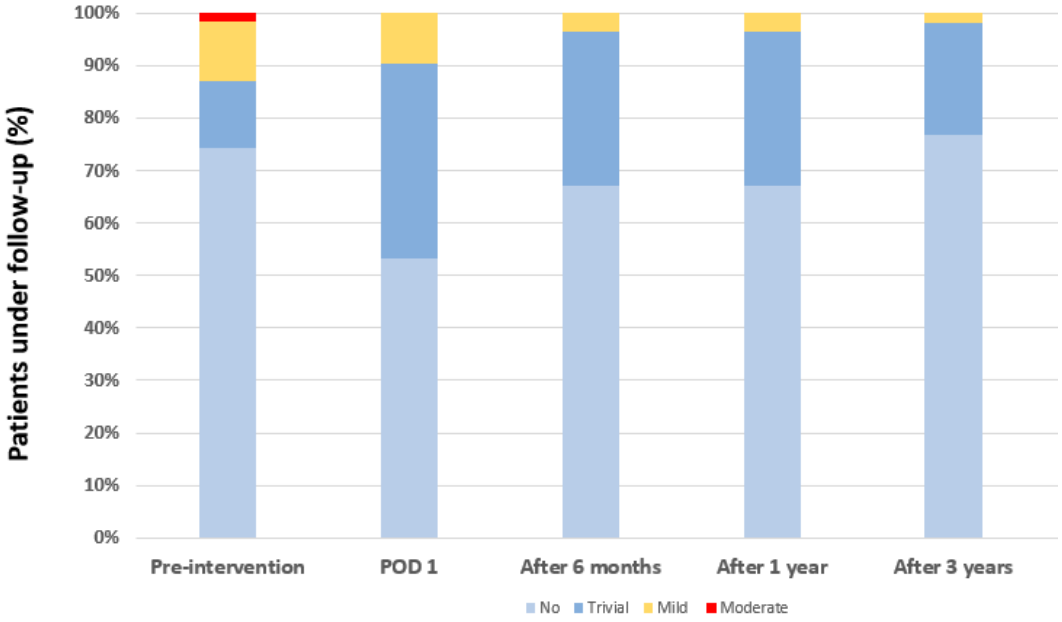
The change of AR during the follow-up period, as illustrated in Figure 3, indicates a decreasing trend in mild and moderate AR following the intervention.

Figure 3. Change of Aortic Regurgitation (AR) Before and After the Intervention



However, even after a minimum follow-up period of 3 years, 6 patients continued to display this AR progression compared to their pre-intervention state, though without further deterioration.

The analysis of the data (Table 6) highlighted that among patients with persistently progressing AR severity, 50% (3/6) were below the age of 4 years, a percentage notably higher than those without such progression (4 out of 56, $p = 0.016$, Fisher's exact test).

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Table 6. Progression of AR after PmVSD Closure for 3 Years

Variable	No progression of AR (*n* = 56)	Progression of AR (*n* = 6)	*P* value
Age (year)*	6.8 (5.3 to 9.2)	5.0 (3.1 to 8.4)	0.216
Age < 4 years	4 (7.1)	3 (50)	0.016
Male	29 (51.8)	5 (83.3)	0.209
BSA (m^2)*	0.9 (0.7 to 1.0)	0.8 (0.6 to 1.1)	0.344
Weight percentile*	49.8 (22.8 to 72.6)	48.4 (16.8 to 81.4)	0.949
Severity of AR			
Trivial or no AR	48 (85.7)	6 (100)	1.0
RCC prolapse	36 (64.3)	5 (83.3)	0.654
PO type VSD	9 (16.1)	3 (50.0)	0.081
Residual shunts after 3 years	9 (16.1)	0 (0)	0.58
VSD diameter on TEE (mm)*	4.0 (3.5 to 5.0)	4.6 (3.3 to 5.8)	0.617
Device diameter / measured diameter*	1.5 (1.3 to 1.7)	1.2 (1.0 to 1.9)	0.276
LVEDD z-score*	0.8 (−0.4 to 1.9)	1.9 (0.2 to 2.9)	0.315
Qp/Qs*	1.3 (1.1 to 1.5)	1.3 (1.2 to 1.6)	0.841
Device type			0.269
ADO	22 (39.3)	1 (16.7)	
ADO II	22 (39.3)	2 (33.3)	
HeartR	12 (21.4)	3 (50)	

Values are numbers (%), or median (interquartile range). * Mann–Whitney U test. AR, aortic regurgitation; BSA, body surface area; RCC, right coronary cusp; PO, perimembranous outlet; VSD, ventricular septal defect; TEE, transesophageal echocardiography; LVEDD, left ventricular end-diastolic diameter; Qp/Qs, pulmonary-to-systemic blood flow ratio; ADO, Amplatzer Duct Occluder; ADO II, Amplatzer Duct Occluder II; HeartR, HeartR pmVSD Occluder.

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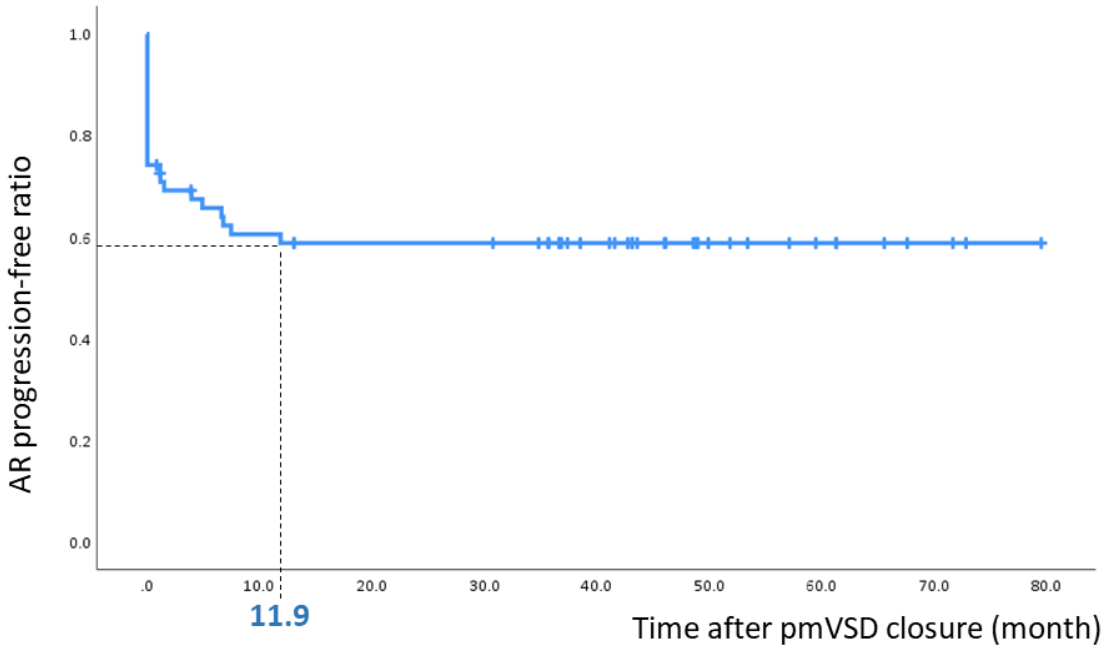
Multivariate logistic regression analysis showed that younger age (<4 years) (OR: 27.38, 95% of CI: 2.33–321.68, $p = 0.008$) and PO type VSD (OR: 11.94, 95% of CI: 1.10–129.81, $p = 0.042$) were both independent risk factors of AR progression 3 years after transcatheter closure.

We also conducted person-time data analysis for AR after VSD closure (Figure 4). None of the enrolled patients experienced a new onset of AR deterioration 11.9 months after the procedure.

Figure 4. The Progression-free Survival of Aortic Regurgitation (AR) Following Transcatheter Closure of Perimembranous Ventricular Septal Defects (pmVSD).



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The analysis using the Cox proportional-hazards model to evaluate the potential risk factor of AR progression (Table 7) revealed that the younger age (<4 years, hazard ratio: 3.10, 95% CI: 1.08–8.86) was the independent risk factor of AR progression after the procedure. The HRs of the usage of ADO (hazard ratio: 3.01, 95% CI: 0.99–9.12, *p* = 0.051), the PO type VSD and the diameter of device minus diameter of pmVSD on TEE greater than 1.5 mm were not statistically significant.

Table 7. Cox Proportional-hazards Model of AR Progression after PmVSD Closure

Variable	HR	95% CI of HR	*P* value
Age < 4 years	3.10	1.08 to 8.86	0.035
PO type VSD	1.40	0.49 to 3.99	0.531
ADO vs. non-ADO	3.01	0.99 to 9.12	0.051
Device diameter minus VSD diameter on TEE ≥ 1.5 mm	0.46	0.15 to 1.40	0.171

HR: hazard ratio, CI: confidence interval, AR: aortic regurgitation, VSD: ventricular septal defect, PO: perimembranous outlet, ADO: Amplatzer Duct Occluder, ADO II: Amplatzer Duct Occluder II, TEE: transesophageal echocardiography

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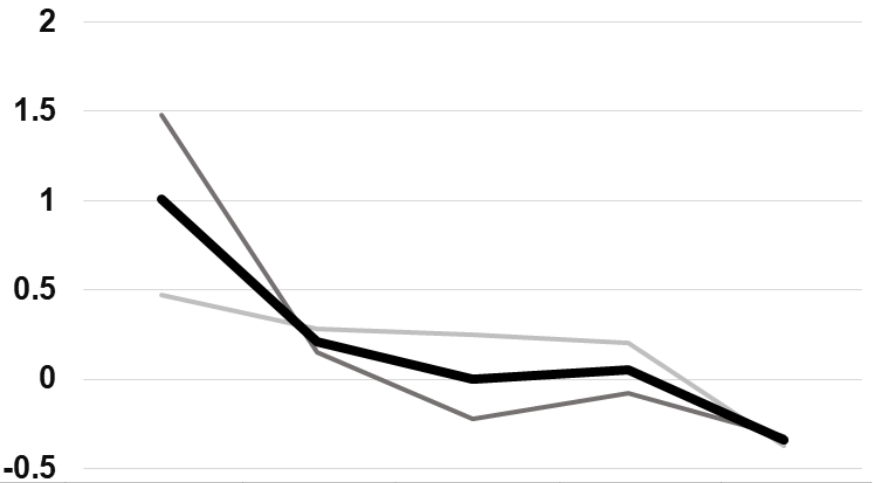
Changes in left ventricular volume after transcatheter closure

The mean LVEDD z-score was 1.01 ± 1.56 before transcatheter closure and −0.34 ± 0.97 one year after the procedure ($p < 0.001$). Figure 5 showed trends of LVEDD z-score: patients with pmVSD demonstrated significant LVEDD improvement one-year post-transcatheter closure, with notable early enhancement at three months observed in those with Qp/Qs exceeding 1.3.

Figure 5. Trends of Left Ventricular End-diastolic Diameter (LVEDD) Z-score.



		Pre-intervention z-score	0–3 months z-score	3–6 months z-score	6–12 months z-score	After 1 year z-score
Total	mean ± SD	1.01 ± 1.56	0.21 ± 1.07	0.00 ± 1.24	0.05 ± 1.11	−0.34 ± 0.97
	95% CI	0.60 to 1.41	−0.07 to 0.49	−0.33 to 0.34	−0.25 to 0.35	−0.61 to −0.08
Qp/Qs ≥ 1.3	mean ± SD	1.48 ± 1.67	0.15 ± 1.18	-0.22 ± 1.26	−0.08 ± 1.17	−0.32 ± 1.00
	95% CI	0.88 to 2.08	−0.28 to 0.58	−0.70 to 0.26	−0.51 to 0.36	−0.72 to 0.07
Qp/Qs < 1.3	mean ± SD	0.47 ± 1.24	0.28 ± 0.94	0.25 ± 1.19	0.20 ± 1.05	-0.37 ± 0.94
	95% CI	−0.01 to 0.94	−0.09 to 0.65	−0.23 to 0.73	−0.23 to 0.63	−0.75 to 0.02

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This significant reduction of LVEDD was detected (Figure 6A and 6D). In subgroup analysis, the reduction of LVEDD was detected not only in patients with Qp/Qs above 1.3 (Figure 6B and 6E) but also in those without (Figure 6E and 6F), although the percentage of patients showing LVEDD improvement differed between the two subgroups (72% in Qp/Qs < 1.3 vs. 96% in Qp/Qs > 1.3, $p = 0.024$).

During the first 3 months after the procedure, the LVEDD z-score decreased significantly in 29 patients with Qp/Qs above 1.3 (z-score difference: -1.28 ± 1.31, $p < 0.001$, Figure 6B). For those with Qp/Qs below 1.3, the LVEDD z-score reduction was not significant until after 1 year (z-score difference: -0.76 ± 1.15, $p = 0.004$, Figure 6F).

Overall, the LVEDD z-score significantly decreased at 3 months (Figure 6A) and one year (Figure 6D). In patients with Qp/Qs above 1.3 (Figure 6B and 6E), a significant reduction in the mean LVEDD z-score was noted. However, for those with Qp/Qs below 1.3, the LVEDD z-score reduction was not significant at 3 months (Figure 6C) but became significant after 1 year (Figure 6F).

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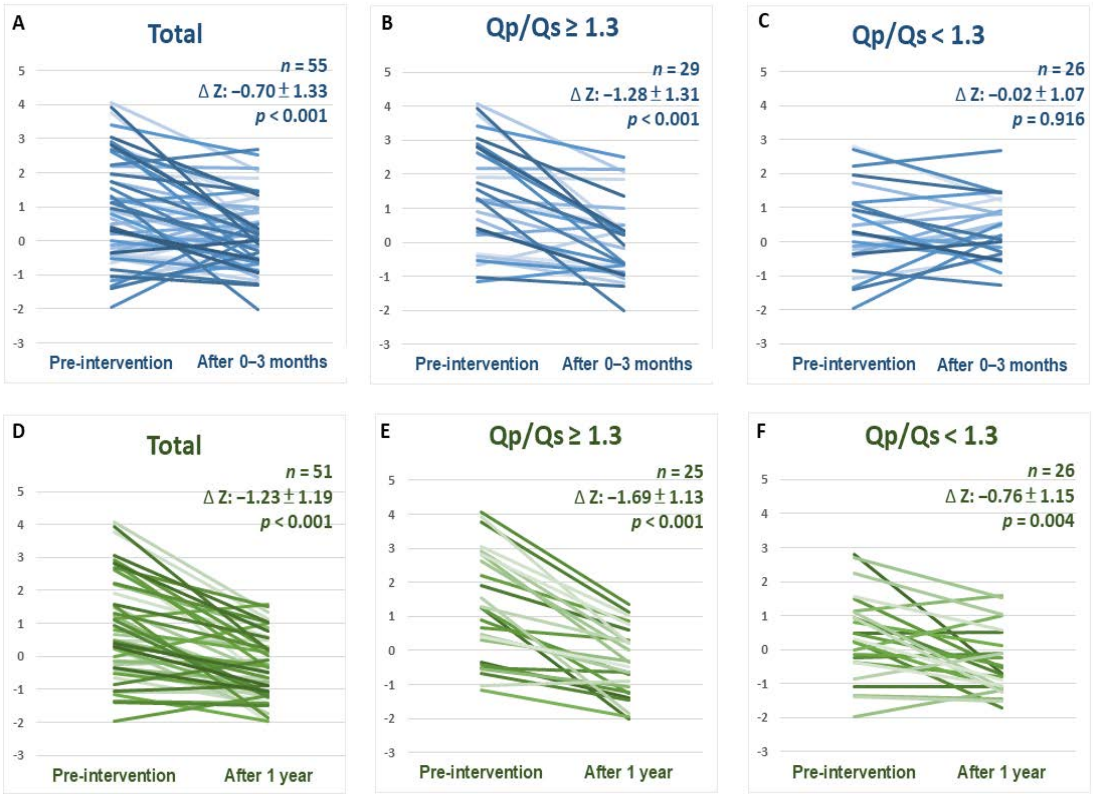
Figure 6. The Mean Reduction in LVEDD z-scores for Both the Overall Patient Cohort and Subgroups.



ΔZ: z-score difference. Qp/Qs: pulmonary-to-systemic blood flow ratio.

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Discussion

In summary of our cohort, we made several important observations. First, using a closure device with a diameter 1.5 mm larger than the VSD diameter resulted in a reduced likelihood of a persistent residual shunt. Second, we observed that 37.1% of patients experienced new or progressive AR after VSD closure. We identified age younger than 4 years and the usage of ADO as risk factors for the development or progression of AR in these patients. Third, we found a significant decrease in the LVEDD z-score after closure of small-to-moderate pmVSD, even in patients with Qp/Qs below 1.3, the reduction in LVEDD z-score was not significant until after 1 year following the procedure.

In previous research[10, 16], it was found that approximately 3.3% to 4.5% of patients with pmVSD experienced the development of new-onset AR following their transcatheter closure. The current study's cohort exhibited a notably higher incidence of new-onset AR, even when categorized as trivial or mild, reaching 37.1% (23 out of 62) within the first day after the procedure, and 9.7% (6 out of 62) at the 3-year mark. This discrepancy could potentially be attributed to the substantial proportion, reaching up to 66.7%, of the present cohort having right coronary cusp prolapse prior to the intervention. In contrast, the study conducted by Jiang D et al. reported that only 3.2% of their analyzed cohort exhibited pre-existing coronary cusp prolapse. Furthermore,

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prior studies have established an association between the presence of coronary cusp prolapse[17] and advanced age[18] in relation to the progression of AR in patients diagnosed with VSD. These findings have led to recommendations for expedited intervention in patients exhibiting these factors. Based on the findings from both the aforementioned and current studies, it may be advisable to recommend that patients with pmVSD and coronary cusp prolapse, yet without concurrent AR, undergo transcatheter closure after reaching the age of four. Employing this targeted subgrouping approach may have the potential to effectively mitigate the risk of new-onset AR associated with the procedure, while also aiding in halting the progression of the disease. This could ultimately result in substantial benefits for the patients.

Although transcatheter closure is safe and uncomplicated in most patients with pmVSD, some patients who experienced cAVB were still noted in previous large cohort studies[7, 10, 16, 19]. Risk factors for the development of cAVB after transcatheter VSD closure included age, weight, VSD location and device type. Jiang D et al.[16] ever reported high up to 25% of the patients with transcatheter closure of pmVSD experienced rhythm or conduction abnormalities early after the procedure. However, in the current cohort with a median age of 6.8 years, no cAVB was detected, and 10 patients (10.8%) had minor rhythm disturbance (complete RBBB in one and incomplete RBBB in nine). The reasons for the relative lower occurrence of rhythm disturbance

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rhythm disturbance may be due to (1) conservative use of devices only 1 to 2 mm larger than the measured diameter of the defects, (2) we deployed the device inside the aneurysmal transformation of the tricuspid valves in most cases, and (3) relatively soft devices deployed in our patients. Multicenter registry is needed to clarify the real risk factors of rhythm disturbance.

Several studies demonstrated the incidence and longitudinal changes of residual shunts after transcatheter pmVSD closure[6, 9, 11, 16, 20]. The incidence of residual shunt after transcatheter closure ranged from 8.3% to 30.8%[9, 11, 16, 20], and one third of the residual shunts diminished gradually during the follow-up[16, 21]. Our cohort not only showed similar results but also clarified the risk factors of persistent residual shunts. Our study revealed that the defect diameter and device size were strongly related to the residual shunts. In logistic regression analysis, the pmVSD diameter greater than 4.5 mm on TEE significantly increased the risk of residual shunts (OR: 6.85, 95% CI: 1.28–36.71, $p = 0.03$). When choosing the device diameter more than the pmVSD diameter on TEE plus 1.5 mm, the risk of residual shunts decreased, though borderline significantly ($p = 0.06$). In residual shunt cases, the probability of disappearance of residual shunts in the patients with a diameter of pmVSD greater than 4.5 mm on TEE was half lower (HR: 0.49, 95% CI: 0.04–0.7), compared with those without. Hence, we could consider choosing a device size that is at least 1.5 mm larger than the pmVSD

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diameter on TEE to minimize the risk of residual shunts, and we should regularly follow-up residual shunt cases with a diameter greater than 4.5 mm after pmVSD closure.

Most patients with small unrepaired VSDs and no LV volume overload on their echocardiography, remain symptom-free, and does not require surgery[4]. However, in a randomized controlled trial of adult VSD, LVEDD normalized after transcatheter closure and surgical repair of VSD at 2 years of follow-up[22]. Children with pmVSD also demonstrated a significant decrease in LVEDD 1 day after transcatheter closure[16]. In the current study, we have further demonstrated the reduction in LVEDD not only in patients with a Qp/Qs ratio greater than 1.3 but also in those with a Qp/Qs ratio less than 1.3. Among the 29 patients including in current study with a Qp/Qs less than 1.3, the indications for pmVSD closure varied. Five of these patients underwent pmVSD closure due to heart failure symptoms, eighteen due to cardiothoracic ratio exceeding 0.5, three because of LV enlargement (LVEDD z-score > 2.0), twenty-one had RCC prolapse, eight had AR, and fourteen patients had multiple reasons mentioned above for pmVSD closure. Significant reduction in LVEDD was not observed until one year following the procedure, and the underlying mechanisms behind this phenomenon remained unclear. Prior researches[23, 24] have indicated that regardless of the size of the shunt, a persistent ventricular septal defect over an extended period may result in

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impaired systolic function and an increase in the compliance of both ventricles due to chronic pressure and volume overload. Abnormal increases in pulmonary vascular resistance and LV end-diastolic pressure, particularly during exercise, were observed, and these may be attributed to the presence of dysplastic cardiac muscle[25]. Collectively, the elimination of the mechanisms mentioned above may contribute to LV remodeling, even over an extended period of time.

Our study has some limitations, such as conducting in a single center, having a retrospective study design, enrolling a small sample size, and failing to compare transcatheter closure with surgical repair in similar patients. Hence, conducting prospective, comparative studies with a longer follow-up time is needed.

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Conclusion

We identified risk factors associated with the development of residual shunts (VSD size > 4.5mm) and AR (< 4 years of age) subsequent to transcatheter closure of pmVSD in young children. It is essential to examine the potential benefits and risks of transcatheter pmVSD closure within this vulnerable subgroup of patients in future investigations.

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Table I. Prevalence and the trend of congenital heart disease in Taiwan, 2000 to 2006, number per 100 000 live births

Diagnosis	Prevalence (95% CI)	*P* value (sex dominance)	*P* value (temporal trend)
Severe CHD	141.5 (135.9-147.3)	<.0001 (M)	<.0001 (D)
TOF	62.6 (58.9-66.5)	.0001 (M)	.0026 (D)
TGA	21.2 (19.1-23.5)	<.0001 (M)	NS
DORV	15.1 (13.3-17.0)	NS	NS
TAPVR	10.6 (9.1-12.2)	NS	NS
Tricuspid atresia	4.6 (3.7-5.8)	NS	NS
CCTGA	2.4 (1.7-3.3)	NS	NS
Common truncus	7.9 (6.7-9.4)	NS	.0037 (D)
Common ventricle	8.4 (7.1-9.9)	NS	NS
HLHS	6.2 (5.1-7.6)	NS	.0251 (D)
Simple CHD	1166.4 (1150.2-1182.8)	<.0001 (F)	<.0001 (D)
VSD	401.4 (391.9-411.1)	.0024 (F)	<.0001 (D)
ASDII	323.3 (314.8-332.0)	<.0001 (F)	<.0001 (D)
PDA	201.2 (194.5-208.1)	<.0001 (F)	<.0001 (D)
PS	121.8 (116.7-127.2)	NS	.0007 (D)
CoA	25.1 (22.8-27.6)	NS	NS
ECD	20.3 (18.2-22.6)	.0022 (F)	.002 (D)
AS	9.2 (7.9-10.9)	NS	.0085 (D)
Ebstein's anomaly	4.7 (3.8-5.9)	NS	NS
Cor triatriatum	1.9 (1.3-2.7)	NS	NS
All CHD	**1307.9 (1290.8-1325.3)**	**<.0001 (F)**	**<.0001 (D)**

AS, Aortic stenosis; *CCTGA*, congenital corrected transposition of great arteries; *D*, decrease; *F*, female; *I*, increase; *M*, male; *NS*, not significant.

Reference: Wu M-H, Chen H-C, Lu C-W, Wang J-K, Huang S-C, Huang S-K. Prevalence of congenital heart disease at live birth in Taiwan. *The Journal of pediatrics*. 2010;156(5):782-785.

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Supplement 2

Transcatheter Closure vs Surgical Closure

Successful Rate

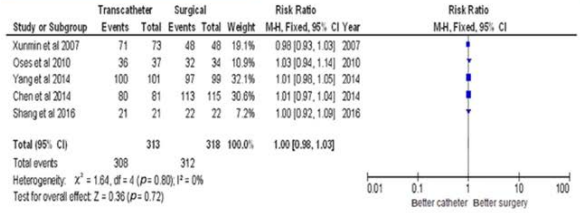

Figure 2. Forest plot of success rate of both procedures. CI = confidence interval.

Overall complications

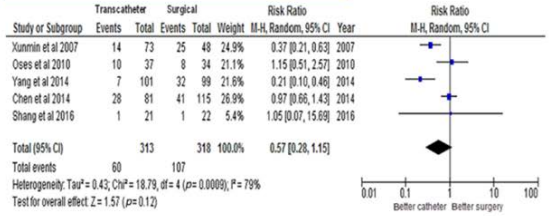

Figure 4. Forest plot of overall complications of both procedures. CI = confidence interval.

El-Kadeem S, et al. Comparison of transcatheter versus surgical closure of perimembranous ventricular septal defect in pediatric patients: A systematic review and meta-analysis. *Journal of the Saudi Heart Association*. 2019;31(4):188-197

Transcatheter Closure vs Surgical Closure

Residual Shunt

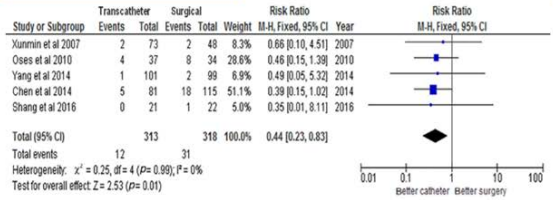

Figure 3. Forest plot of residual shunt after both procedures. CI = confidence interval.

Complete AV Block

Figure 5. Forest plot of complete atrioventricular block (CAVB) after both procedures. CI = confidence interval.

Blood Transfusion

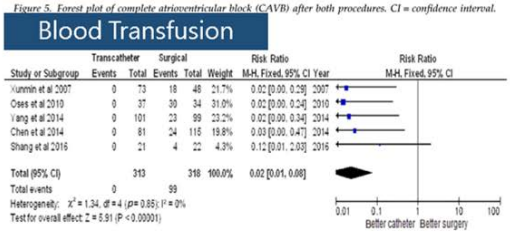

Figure 6. Forest plot of need for blood transfusion in both procedures. CI = confidence interval.

El-Kadeem S, et al. Comparison of transcatheter versus surgical closure of perimembranous ventricular septal defect in pediatric patients: A systematic review and meta-analysis. *Journal of the Saudi Heart Association*. 2019;31(4):188-197

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