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Clinical Research

Characteristics of Patients with Surgical Closure of an Atrial Septal Defect during Infancy

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Background: Surgical closure of an atrial septal defect (ASD) is infrequently indicated during infancy. We evaluated the clinical characteristics and outcomes of patients who underwent surgical ASD closure during infancy.
Methods: A single-center retrospective review was performed for 39 patients (19 males) who underwent surgical ASD closure during infancy between 1993 and 2020. The median body weight percentile at the time of operation was 9.3.
Results: During a median follow-up of 60.9 months, 4 late deaths occurred due to chronic respiratory failure. A preoperative history of bronchopulmonary dysplasia (BPD) was the only risk factor for late mortality identified in Cox regression (hazard ratio, 3.54; 95% confidence interval [CI], 1.75–163.04; p=0.015). The 5-year survival rate was significantly lower in patients with preoperative history of BPD (97.0% vs. 50.0%, p<0.001) and preoperative ventilatory support (97.1% vs. 40.4%, p<0.001). There were significant postoperative increases in left ventricular end-diastolic (p=0.017), end-systolic (p=0.014), and stroke volume (p=0.013) indices. A generalized estimated equation model showed significantly better postoperative improvement in body weight percentiles in patients with lower weight percentiles at the time of operation (<10th percentile, p=0.01) and larger indexed ASD diameter (≥45 mm/m^2, p=0.025).
Conclusion: Patients with ASD necessitating surgical closure during infancy are extremely small preoperatively and remain small even after surgical closure. However, postoperative somatic growth was more prominent in smaller patients with larger defects, which may be attributable to an increase in postoperative cardiac output due to changes in ventricular septal configuration. The benefits of ASD closure in patients with BPD are undetermined.

Keywords: Congenital heart defects, Atrial heart septal defects, Bronchopulmonary dysplasia, Pediatric cardiology, Infancy

Introduction

Atrial septal defect (ASD) is a common form of congenital heart defect, representing approximately 7.5% of all cases of congenital cardiac disease. In most cases, ASD is well tolerated and usually asymptomatic during infancy or early childhood, and surgical closure is not frequently indicated during the first year of life. However, some individuals with symptoms of heart failure or pulmonary hypertension (PHT) do not respond to medical treatment, necessitating surgical intervention during infancy [1]. It has previously been reported that ASD could be associated with PHT in preterm infants with moderate or severe bronchopulmonary dysplasia (BPD) or in infants who had been severely small for gestational age [2,3]. Early surgical repair of ASD for infants with poor tolerance has been known to improve clinical performance, growth, and development [4]. However, the benefits or risks of ASD closure during infancy remain unclear, particularly in patients with BPD or delayed growth. This study was conducted to assess the clinical characteristics of infantile ASD closure and to determine postoperative somatic growth and changes in echocardiographic findings.

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Methods

Patients

A retrospective review of 39 patients with ASD who underwent surgical correction during infancy between 1993 and 2020 was performed. This subset accounted for 1.8% (39/2,150) of overall surgical series of ASD closure during the same timeframe. Patients with other cardiac anomalies, except for patent ductus arteriosus, were excluded from the study cohort. There were 19 boys and 20 girls, and 9 patients (9/39, 23.1%) were born prematurely (i.e., gestational age <37 weeks). ASD was diagnosed prenatally in 9 patients (9/39, 23.1%). The median birth weight in kilograms and in percentiles was 2.88 kg (interquartile range [IQR], 2.42–3.20 kg) and the 19.1 percentile (IQR, 2.4–38.5 percentile), respectively. The median body weight percentile decreased significantly postnatally to the 9.3 percentile (IQR, 0.1–33.6 percentile; p=0.032) at the time of operation. Thirteen patients (13/39, 33.3%) needed neonatal intensive care after birth, and 5 patients (5/39, 12.8%) received mechanical ventilatory support preoperatively. Chromosomal anomalies were present in 5 patients (5/39, 12.8%): Down syndrome in 3 patients, Noonan syndrome in 1 patient, and Dandy-Walker variant in 1 patient. A preoperative history of BPD was present in 6 patients (6/39, 15.4%) [5]. The indications for early surgical intervention were a history of BPD or chronic lung disease (n=7), failure to thrive (n=15), frequent respiratory infection (n=3), and a large ASD not amenable to interventional closure (n=13). Data collection, collation, and analysis were approved by institutional review boards (IRB registration number: S2022-1418-0001; IRB approval date: 2022/11/4), and the acquisition of informed consent from patients was waived due to the retrospective nature of the study.

Echocardiographic evaluation

Retrospective review of echocardiographic images was conducted using the TomTec software (Image Arena VA ver. 4.6; TomTec Imaging Systems, Unterschleissheim, Germany). Tricuspid valve regurgitation (TR) peak flow velocity was measured as a surrogate marker for systolic pulmonary arterial pressure. Preoperative PHT (i.e., TR velocity ≥3 m/sec) was present in 20 patients (20/39, 51.3%), absent in 9 patients (9/39, 23.1%), and unknown in 10 patients (10/39, 25.6%). Both preoperative and postoperative echocardiographic data of left ventricular dimensions and volumes, including left ventricular end-diastolic internal dimension index (LVIDdI), left ventricular end-systolic internal dimension index (LVIDsI), left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and left ventricular stroke volume index (LVSVI) were achievable in 22 patients (22/39, 56.4%).

Statistical analysis

Categorical variables were presented as frequencies and percentages, and continuous variables were presented as mean with standard deviation or median with IQR according to the distribution of the data. Distributional normality was tested using the Kolmogorov-Smirnov method. Postoperative changes of left ventricular dimensions and volumes were compared using the Wilcoxon signed rank test. Kaplan-Meier survival estimation was used for the analysis of time-related deaths, and differences between the subgroups were tested using the log-rank test. To identify risk factors for decreased time to death after ASD closure, the Cox proportional hazards model was fitted. Risk factors with a p-value less than 0.1 on univariable analysis were input into the multivariable model. Time-related changes in body weight percentile with inter-group differences were analyzed using the generalized estimating equation (GEE) method. Statistical analysis was conducted with IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA), R software ver. 3.4.4 (https://www.r-project.org/), and GraphPad statistical software package ver. 5 (GraphPad Software, San Diego, CA, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Operative characteristics

The median age, body weight in kilograms, and body weight in percentile at operation were 7.7 months (IQR, 4.6–10 months), 7.1 kg (IQR, 6.0–8.8 kg), and the 9.3 percentile (IQR, 0.1–33.6 percentile), respectively. The morphological type of ASD was ostium secundum defect in all patients. The median diameter of the ASD measured at the operating field indexed to the body surface area (BSA) was 45.5 mm/m^2 (IQR, 35.7–55.6 mm/m^2). The patch materials used for the surgical closure of ASD were fresh (n=17) or glutaraldehyde-fixed (n=19) autologous pericardium, bovine pericardium (n=1), and 0.5 mm thick polytetrafluoroethylene patch (Gore-Tex Acuseal patch; W. L. Gore & Associates, Flagstaff, AZ, USA) (n=1). One patient underwent

primary repair of the ASD. Median postoperative ventilator support time, intensive care unit stay, and hospital stay were 12.5 hours (IQR, 7–50 hours), 2 days (IQR, 1–5 days), and 6 days (IQR, 5–10 days), respectively.

Risk factors for late death and survival

There were 4 late deaths during the median follow-up duration of 60.9 months, attributable to chronic respiratory failure. Table 1 shows the clinical characteristics of the 4 patients with postoperative mortality. Patients with late mortality were characterized by low birth weight and higher associations of prematurity, BPD, and PHT. Cox regression analysis (Table 2) identified preoperative ventilator support (hazard ratio [HR], 21.8; p=0.008), chromosomal abnormality (HR, 6.23; p=0.067), preoperative BPD (HR, 16.88; p=0.015), and BSA at operation (HR, 0.00; p=0.082) as risk factors for late death on univariable analysis. However, multivariable analysis identified preoperative BPD as the only risk factor for late death (HR, 3.54; p=0.015). Fig. 1 presents the Kaplan-Meier survival curve. Postoperative survival at 10 years was 89.5% in the whole cohort (Fig. 1A). Survival at 5 years was better in patients without BPD (Fig. 1B) and without preoperative mechanical ventilatory support (Fig. 1C).

Echocardiographic follow-up

All values of left ventricular dimensions and volumes increased postoperatively; however, changes in LVIDdI (p=

Table 1. Clinical characteristics of the 4 patients with postoperative mortality

No.	Sex	Birth weight (kg)	Prematurity (GA <37 wk)	Genetic abnormality	BPD	PHT	Age at operation (mo)	Body weight at operation (percentile)	Postoperative age at death (mo)	Causes of death
1	M	2.3	(+)	(+)	(+)	(+)	2.8	0	8.8	Sepsis
2	M	2.5	(-)	(-)	(-)	Unknown	4.0	0	8.1	Respiratory failure
3	M	2.9	(-)	(+)	(+)	(+)	4.0	3.1	12.9	Respiratory failure
4	F	0.9	(+)	(-)	(+)	(+)	8.6	16	13.8	Respiratory failure

GA, gestational age; BPD, bronchopulmonary dysplasia; PHT, pulmonary hypertension; M, male; F, female.

Table 2. Cox regression analysis for mortality after 30-day after surgery after ASD closure during infancy

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex (male)	3.32 (0.35–32.0)	0.30		
Birth weight (percentile)	0.92 (0.83–1.02)	0.12		
Prenatal diagnosis	1.13 (0.12–10.90)	0.91		
Prematurity (GA <37 weeks)	3.89 (0.55–27.66)	0.18		
Preoperative ventilator support[a]	**21.8 (2.25–211.39)**	**0.008**		
Chromosomal abnormality[a]	**6.23 (0.88–44.31)**	**0.067**		
Preoperative BPD[a]	**16.88 (1.75–163.04)**	**0.015**	**3.54 (1.75–163.04)**	**0.015**
Preoperative PHT	0.36 (0.33–30.12)	0.323		
Age at operation (month)	0.76 (0.54–1.07)	0.30		
Body weight at operation (kg)	0.63 (0.35–1.11)	0.11		
Height at operation (cm)	0.89 (0.80–1.0)	0.053		
BSA at operation (m^2)[a]	**0.00 (0.00–4.80)**	**0.082**		
Indexed ASD size (mm/m^2)	1.01 (0.96–1.06)	0.65		
CPB time (min)	1.01 (0.98–1.05)	0.61		
ACC time (min)	1.03 (0.97–1.09)	0.30		

ASD, atrial septal defect; HR, hazard ratio; CI, confidence interval; GA, gestational age; BPD, bronchopulmonary dysplasia; PHT, pulmonary hypertension; BSA, body surface area; CPB, cardiopulmonary bypass; ACC, aortic cross-clamping.
[a]Variables in bold letters were input to the multivariable model. Because of the collinearity between preoperative ventilator support and preoperative BPD, and because of the higher clinical implication of the latter variable, the presence of BPD was selected as a variable for the multivariable model.

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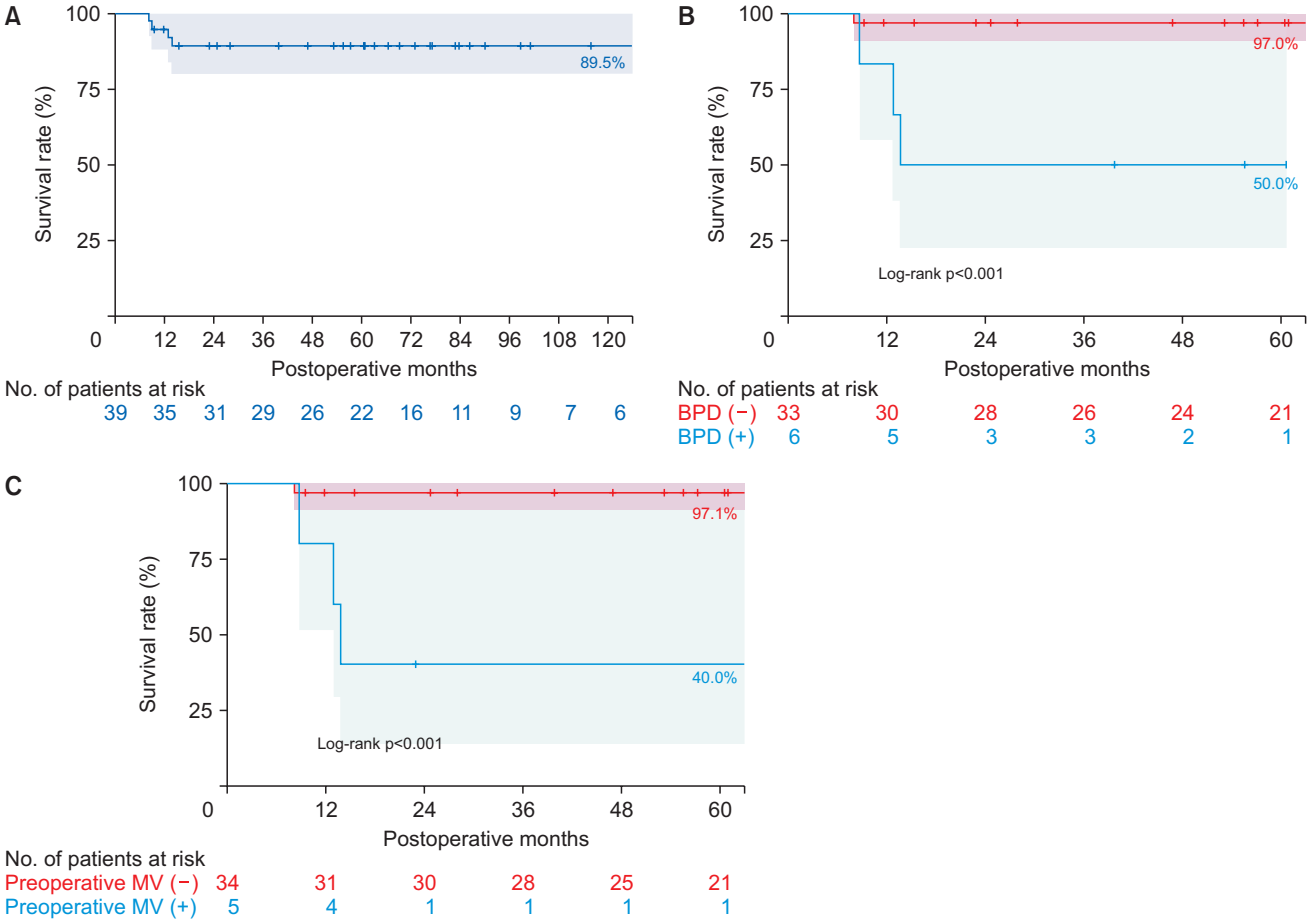

Fig. 1. Kaplan-Meier survival estimates with 95% confidence interval in the entire cohort (A), in the groups with or without a preoperative history of bronchopulmonary dysplasia (BPD) (B), and in the groups with or without preoperative mechanical ventilator support (C). MV, mechanical ventilator.

0.12) and LVIDsI (p=0.24) were statistically insignificant. Postoperative increases in LVEDVI (p=0.017), LVESVI (p=0.014), and LVSVI (p=0.013) were statistically significant (Fig. 2).

Weight gain

Fig. 3 shows postoperative time-related changes in body weight percentiles in the whole cohort and subgroups. The body weight increase after operation was insignificant (p=0.15) in the GEE analysis in the entire group (Fig. 3A). When the cohort was divided into subgroups with or without a preoperative history of BPD (Fig. 3B), time-related changes in body weight percentiles appeared to be better after ASD closure in patients without BPD, although the difference did not reach statistical significance (p=0.067). The postoperative increase in body weight percentiles was significantly more favorable in patients with lower body weight percentile (<10th percentile) at operation (p=0.010) (Fig. 3C) and larger indexed ASD diameter (≥45 mm/m^2) (p=0.025) (Fig. 3D).

Discussion

Since patients with ASD are usually asymptomatic during infancy, closure of isolated ASD is generally indicated at preschool age. However, there is a subset of patients presenting early development of congestive heart failure and requiring early surgical repair [1,6,7]. Because even a minor intracardiac shunt might be poorly tolerated during infancy in patients with compromised pulmonary function, early surgical ASD closure could prevent the early onset of irreversible pulmonary vasculature changes and overcome failure to thrive [4,8-10]. In this study, postoperative survival at 10 years was 89.5%, which is excellent, although 4 late deaths attributable to chronic lung failure oc-

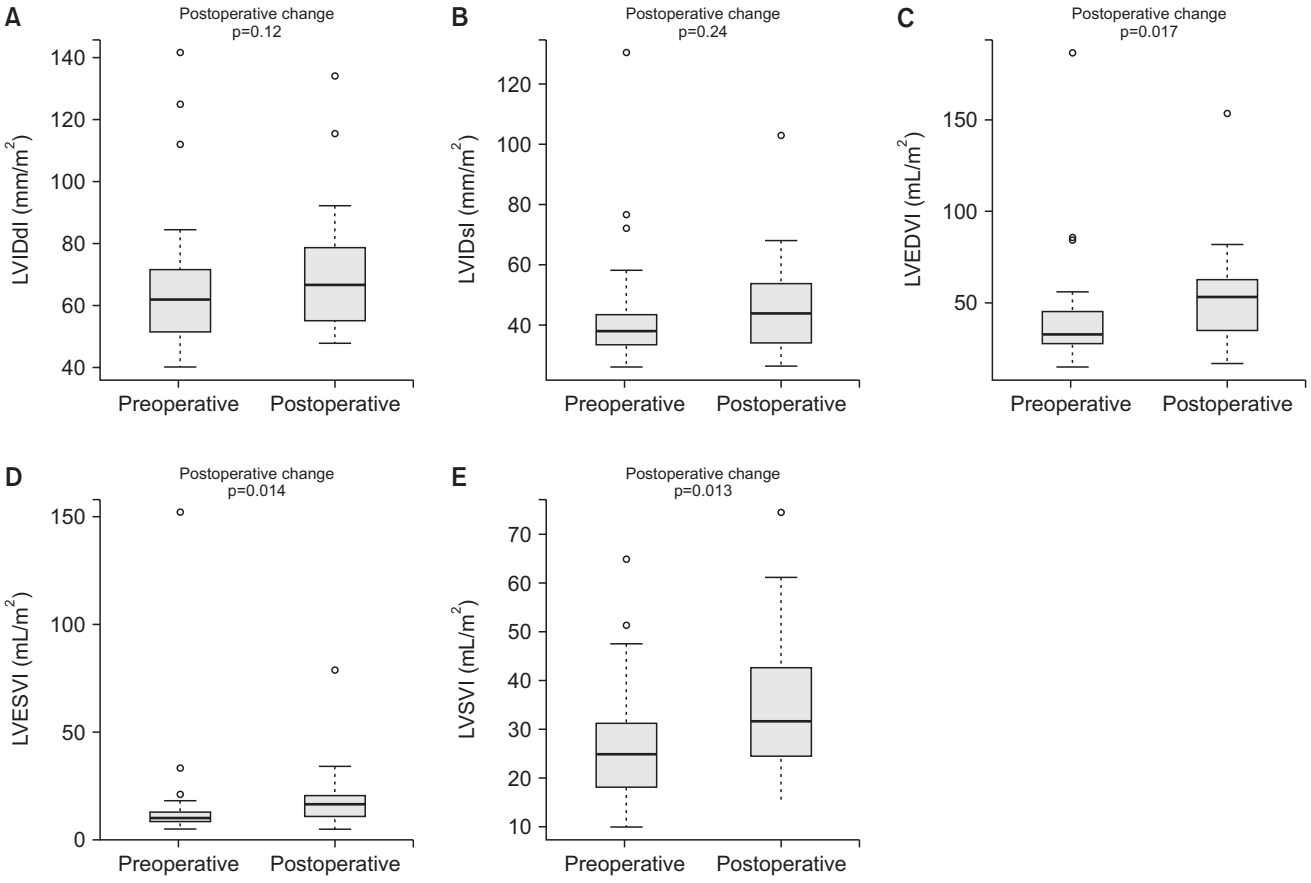

Fig. 2. Postoperative changes in left ventricular end-diastolic internal dimension index (LVIDdI) (A), left ventricular end-systolic internal dimension index (LVIDsI) (B), left ventricular end-diastolic volume index (LVEDVI) (C), left ventricular end-systolic volume index (LVESVI) (D), and left ventricular stroke volume index (LVSVI) (E). The upper and lower whiskers represent the maximum and minimum values excluding outliers, and the upper and lower borders of the boxes represent the upper and lower quartiles. The horizontal lines inside the boxes and open circles denote the median values and the outliers, respectively.

curred. An earlier report of a significant association between ASD and PHT in preterm infants with moderate or severe BPD made it possible to assume that patients with BPD could benefit from early surgical repair of ASD [2]. Because there were 3 late deaths among the 6 patients with a history of BPD, however, the benefits of ASD closure in infants with BPD remain undetermined. Furthermore, an increase in body weight percentile in patients with BPD was insignificant compared to the subset without BPD, which also casts doubt on the benefits of ASD closure in patients with BPD.

However, patients with a lower body weight percentile (<10th percentile) at the time of operation and a larger indexed ASD diameter (≥45 mm/m^2) showed a significant postoperative increase in body weight percentile. This could be explained by the hemodynamic mechanism of the postoperative improvement in cardiac output after ASD closure. We observed significant increases in left ventricular volume indices after surgical repair of ASD, which coincides with the previous observation that postoperative changes in ventricular septal geometry after ASD closure (i.e., restoration of diastolic rightward convexity of the ventricular septum) might contribute to the increase in cardiac output [11].

Limitations

The main limitation of this study arises from its retrospective design. The sample size was relatively small, and echocardiographic follow-up was incomplete or irregular for some patients.

Conclusion

Patients with ASD who require surgical closure during infancy are very small before surgery and remain small

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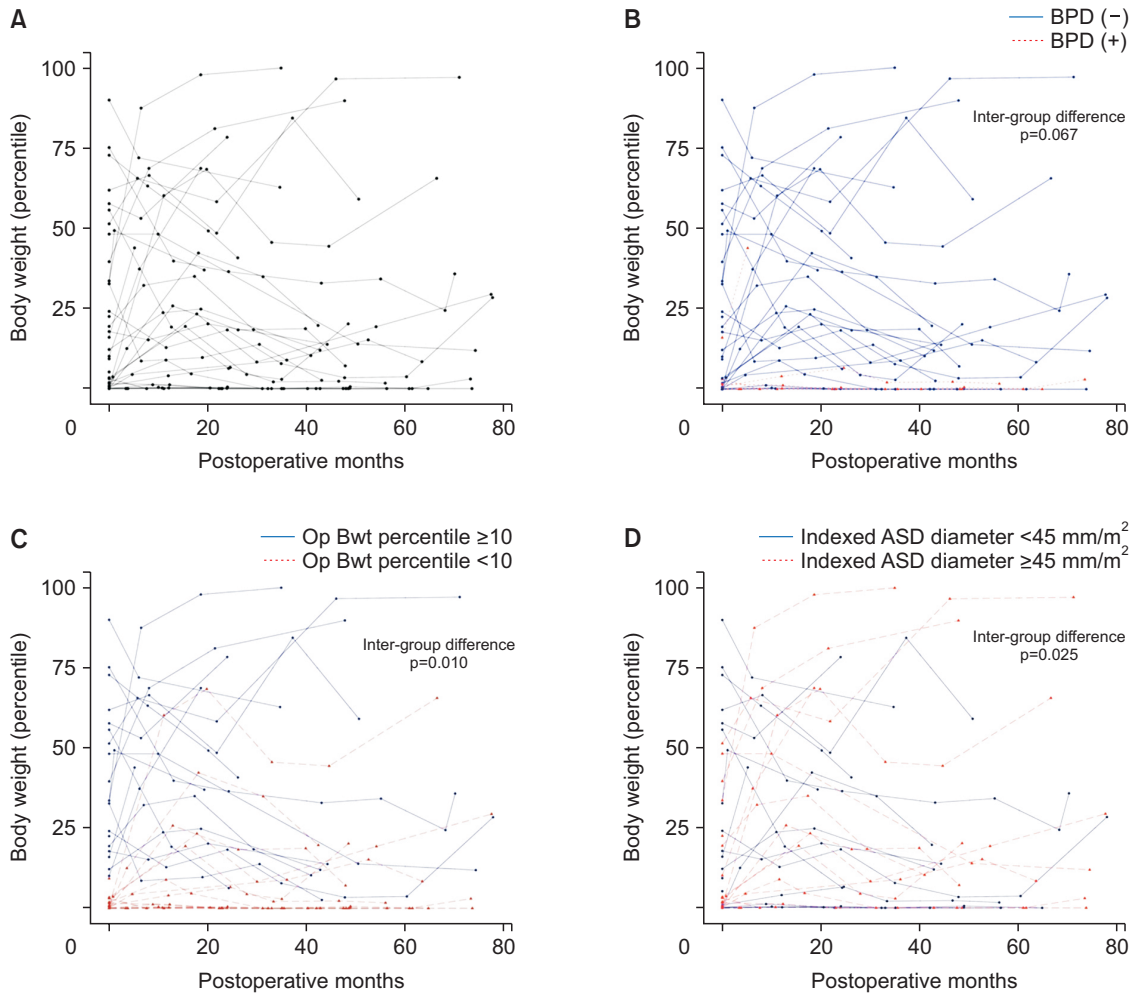

Fig. 3. Postoperative time-related changes in body weight (Bwt) percentiles in the whole cohort (A), in the groups with or without a preoperative history of bronchopulmonary dysplasia (BPD) (B), in the groups whose Bwt percentiles at the time of operation were under or over 10 (C), and in the groups whose atrial septal defect (ASD) diameters indexed to body surface area were under or over 45 mm/m^2 (D). OP, operative.

even after surgery. However, in smaller patients with larger defects, postoperative somatic growth was relatively more significant. This may be attributable to an increase in postoperative cardiac output due to changes in the ventricular septal configuration. The benefits of ASD closure in patients with BPD are undetermined.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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