Cardiology in the Young

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Risk factors for adverse events within one year after atrial septal closure in children: a retrospective follow-up study

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Abstract

Introduction: Secundum atrial septal defect is one of the most common congenital heart defects. Previous paediatric studies have mainly addressed echocardiographic and few clinical factors among children associated with adverse events. The aim of this study was to identify neonatal and other clinical risk factors associated with adverse events up to one year after closure of atrial septal defect. *Methods:* This retrospective case–control study includes children born in Sweden between 2000 and 2014 that were treated surgically or percutaneously for an atrial septal defect. Conditional logistic regression was used to evaluate the association between major and minor adverse events and potential risk factors, adjusting for confounding factors including prematurity, neonatal sepsis, neonatal general ventilatory support, symptomatic atrial septal defects, and pulmonary hypertension. *Results:* Overall, 396 children with 400 atrial septal defect closures were included. The median body weight at closure was 14.5 (3.5–110) kg, and the median age was 3.0 (0.1–17.8) years. Overall, 110 minor adverse events and 68 major events were recorded in 87 and 49 children, respectively. Only symptomatic atrial septal defects were associated with both minor (odds ratio (OR) = 2.18, confidence interval (CI) 95% 1.05–8.06) and major (OR = 2.80 CI 95% 1.23–6.37) adverse events. *Conclusion:* There was no association between the investigated neonatal comorbidities and major or minor events after atrial septal defect closure. Patients with symptomatic atrial septal defects had a two to four times increased risk of having a major event, suggesting careful management and follow-up of these children prior to and after closure.

A secundum atrial septal defect is located in the central portion of fossa ovalis and is one of the most common congenital heart defects.[1] Moderate to large atrial septal defect is associated with significant left-to-right shunts and subsequent increase in pulmonary blood flow. This right-side volume overload of the heart may induce symptoms such as failure to thrive, tachypnoea, or recurrent infections.[2,3] Haemodynamically significant atrial septal defects seldom present with symptoms and are preferably closed electively when the child has reached the age of three to 4 years.[4,5] However, symptomatic atrial septal defects, especially combined with other cardiac or premature comorbidities, may need to be closed earlier. Today, there is no consensus concerning the timing of atrial septal defect closure among these children.

Six percent of all children born in Sweden are born preterm.[6,7] Modern perinatal care has led to improved survival.[8,9] Children born preterm have altered cardiac morphological structures as well as functional impairment of their heart, withstanding into adulthood, and sometimes along with additional cardiac and pulmonary sequelae.[10–13] These cardiac alterations and comorbidities may influence these children's vulnerability to complications when going through procedures later in life.

A shift towards an early atrial septal defect closure in young and small children with symptomatic atrial septal defects have been noted by us and others.[3,14,15] Early atrial septal defect closure is considered safe and may be beneficial for pulmonary recovery in preterm children.[16,17] However, few studies have assessed the association between the risk of adverse events following an atrial septal defect closure and preterm morbidity.

We hypothesised that preterm children are at risk for adverse events following atrial septal defect closure (surgical and percutaneous device closure) due to the complex comorbidity and additional cardiac remodelling. The main objective of this study was to explore potential neonatal and clinical factors associated with both major and minor events within 1 year after atrial septal defect closure.

Materials and methods

This is a retrospective case–control study including children under the age of 18 years who were born in Sweden and treated with an atrial septal defect closure (surgery or percutaneous device

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Table 1. Potential clinical risk factors and confounding factors

Risk factors	Grouped risk factors
Additional CHD	
Chromosomal defects	
Preterm	
Late premature	Preterm >32 to <37 gestational age
Very premature	Preterm <32 weeks of gestational age (*Very preterm + extreme preterm)*
Extreme premature	
Pulmonary disease*	Pulmonary diseases and general ventilatory support (*Pulmonary disease + IRDS + BPD + Neonatal respiratory ventilation + Neonatal CPAP*)
IRDS	
BPD	
Neonatal respiratory ventilation	
Neonatal CPAP	
Neonatal sepsis	Neonatal sepsis
Pulmonary hypertension	Pulmonary hypertension
Symptomatic ASD	Symptomatic ASD

ASD = atrial septal defect; BPD = bronchopulmonary dysplasia; CHD = congenital heart defects; CPAP = continuous positive airway pressure; IRDS = infant respiratory distress syndrome.
*Pulmonary disease includes: Transient tachypnoea of the new-born, IRDS, BPD, Pneumothorax and Congenital Diaphragmatic Hernia.

closure) between January 2000 and December 2014 at Skåne University Hospital in Lund and Astrid Lindgren Children's Hospital at Karolinska University Hospital in Stockholm.

Children born abroad were excluded, as they are not included in the Swedish Medical Birth Registry and thereby missing important demographic data.

All surgeries were performed at Skåne University Hospital in Lund, and the percutaneous device closures were performed at both centres.

Cases were defined as children with one or more adverse events (either major or minor event), and controls were defined as children without adverse events. Factors related to the atrial septal defect, neonatal as well as cardiac morbidity and chronic pulmonary disease were taken into account as confounding factors (Table 1). Preterm children were stratified according to the World Health Organization definition of gestational age at birth, late premature (32 to <37), very premature (28 to <32 weeks), and extreme premature (<28 weeks).

Demographic data, potential risk factors, and adverse events were retrieved from medical records, the Swedish Registry of Congenial Heart Disease,[18] and Swedish Medical Birth Register[19] (Table 1). Adverse events were categorised according to severity and were presented in detail in a previous publication.[20]

The risk factor "Symptomatic atrial septal defects" was used when stated in the medical journal as diagnoses related to heart failure according to International classification of disease (ICD 10 I50.0-9) and/or if the child was treated with antidiuretic drugs.[21,22]

The risk factor "pulmonary hypertension" was used when echocardiographic findings indicated a systolic right ventricular pressure ≥25 mmHg, by measures of the tricuspid regurgitant velocity > 2.6 m/second, or when invasive catheter measurements showed a mean pulmonary artery pressure of ≥25 mmHg pulmonary or a pulmonary vascular resistance of ≥3 WU × m^2, all prior to the atrial septal defect closure.[23]

Definitions of study group inclusion criteria and cases with conversion from percutaneous device closure to surgery

In 41 children who underwent atrial septal defect catheterisation with intention to treat the atrial septal defect, the procedure was converted to surgery due to unfavourable anatomy or insufficient rims. These children were included in the surgical group, and the conversion was not recorded as an adverse event.

In six children, major adverse events requiring surgery (persistent arrhythmias (n = 4), device embolisation (n = 1), and significant residual shunt (n = 1)) occurred after or during percutaneous device closure. These children required device removal and surgical closure of the defect. They were primarily included in the percutaneous device closure group, and the need of surgery was recorded as an adverse event and then additionally included in the surgical group.

Overall, 419 atrial septal defect closures were identified; 266 closed percutaneously and 153 surgically (Fig 1).

Statistical analyses

All data are presented as mean (SD), median (range), or percentage (%) depending on the type and distribution of the data. Continuous data were primarily tested for normality using Shapiro-Wilks test. Student's t-test (unpaired two-sided) was used for parametrically distributed variables, Mann-Whitney U test for non-parametric distributed variables, and Person's χ^2 for categorical data, with $p < 0.05$ considered to be significant.

Conditional logistic regression was performed to evaluate the association between major and minor adverse events and potential risk factors (Table 1). Maximum-likelihood estimates of the OR and 95% CI were obtained, taking into account potential confounding factors.

Univariate logistic regression was performed for both major and minor adverse events and performed for three categories:

1. All atrial septal defect closures
2. Children with percutaneous device closure of atrial septal defect
3. Children with surgical atrial septal defect closure

Conditional logistic regression was performed to evaluate the association between potential risk factors and major as well as minor adverse events following atrial septal defect closure. In this model, additional congenital heart defects and chromosomal defects were excluded as potential risk factors, and all potential synergistic neonatal and clinical factors were grouped according to clinical relation (Table 1). This model was used to reduce the risk of overadjustment and to emphasise clinically linked risk factors.

Results

Overall, 511 children underwent atrial septal defect closure performed at either one of our two centres. A total of 117 children were excluded from the study group due to invalid identification numbers, having been born abroad or declined participation, leaving 394 individual children and 400 individual atrial septal defect closures for analysis (Fig 1).

General characteristics

The median body weight for children with an atrial septal defect closure was 14.5 kg (3.5–110 kg), the median age was 3.0 years

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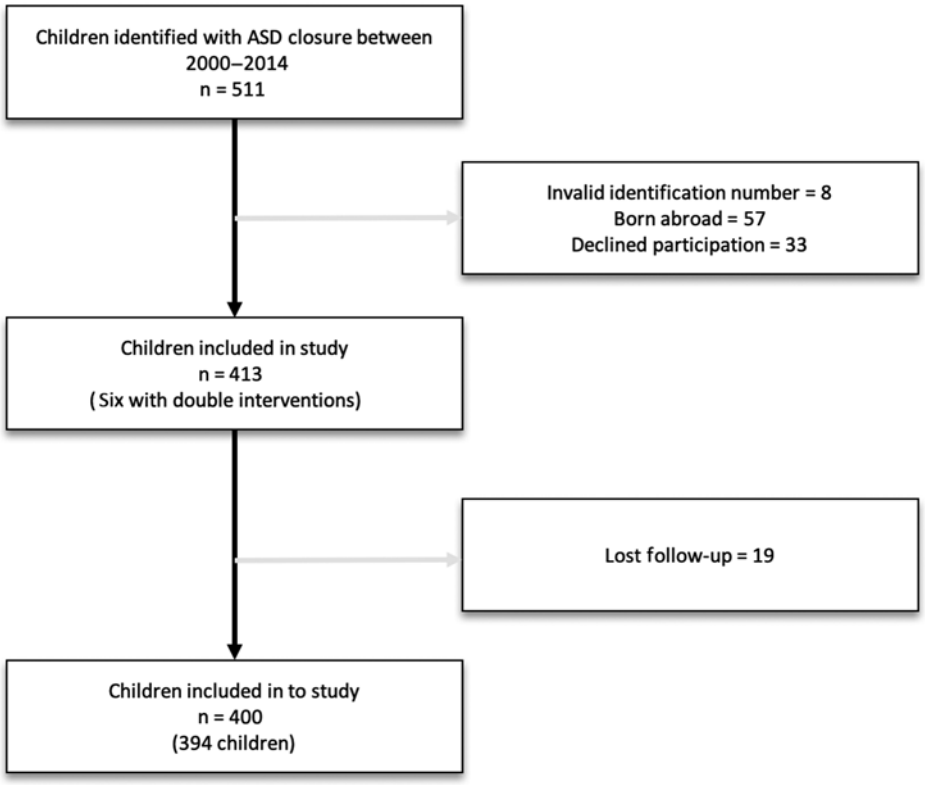

Figure 1. Included children.

(0.1–17.8 years), the median atrial septal defect size 13.0 mm (4.1–37.0 mm), and the median atrial septal defect-to-weight ratio 0.9 mm/kg (0.1–4.3) (Table 2). The female:male ratio was 1.5:1. Further demographic data are presented in Table 3.

Adverse events

Overall, 110 minor adverse events in 87 children and 68 major events in 49 children were recorded. The most common major events were persistent arrhythmias or intraprocedural arrhythmias requiring treatment, accounting for 25 (36.7%) of all major events. Three types of minor events were predominantly common; 34 cases of suspected infection (30.9%), 32 cases with trivial pericardial/pleural effusion (29.1%), and 12 cases of arrhythmias not requiring treatment (10.9%) (Table 4).

Deaths

Four children died during the follow-up period. One 17-year-old child underwent an electrophysiological ablation one day prior to the atrial septal defect closure where a 27 mm Amplatzer septal occlude was used. She died on the 5th day after device placement due to device erosion and pericardial effusion. One child with surgical atrial septal defect closure, at the age of 13 months, died 237 days after surgery due to ventricular arrhythmia. A 12-month-old child with hypertrophic cardiomyopathy died 166 days after surgical atrial septal defect closure due to septic shock. One preterm child, born at a gestational age of 22 weeks, had a surgical atrial septal defect closure at the age of 6 months and died 27 days after surgery due to pulmonary hypertension crisis and multiple organ failure.

Associations between risk factors and adverse events. Univariate regression model and distribution

None of the sub-groups of premature birth were associated with neither minor nor major events, regardless of type of atrial septal defect closure (Table 3).

Some neonatal comorbidities that are common among children born prematurely were more common in cases with major events compared to controls. There were, for example, more cases with pulmonary disease (10 cases (22.2%) versus 34 controls (9.8%), $p = 0.013$), infant respiratory distress syndrome (IRDS) (6 cases (13.3%) versus 19 controls (5.5%), $p = 0.042$), need of neonatal respiratory ventilation (8 cases (17.8%) versus 13 controls (3.7%), $p < 0.001$), neonatal continuous positive airway pressure (CPAP) (12 cases (26.7%) versus 35 controls (10.1%), $p < 0.001$), and neonatal sepsis (6 cases (13.3%) versus 18 controls (5.2%), $p = 0.031$)(see Table 3).

Many of these factors also showed increased risks for adverse events in univariate regression analysis (see Table 3–5).

Especially among children with surgically closed atrial septal defect, risk factors such as neonatal pulmonary disease (OR = 4.90 CI 95% 1.62–14.84), bronchopulmonary dysplasia (OR = 5.10 CI 95% 1.07–24.10), need of neonatal respiratory ventilation (OR = 3.93 CI 95% 1.06–14.55), neonatal CPAP (OR = 2.75 CI 95% 1.01–7.47), symptomatic atrial septal defects (OR = 5.39 CI 95% 2.20–13.19), pulmonary hypertension (OR = 5.83 CI 95% 1.81–18.38), and additional congenital heart defects (OR = 2.27 CI 95% 1.02–5.05) were all associated with major adverse events in the univariate conditional regression analyses (Table 4).

Among children with percutaneously closed atrial septal defect, neonatal respiratory ventilation (OR = 6.16 Cl 95% 1.47–25.80)

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Table 2. Study population

	Demography study population			
	Total individuals (n = 400)	Percutaneous device closure (n = 257)	Surgery (n = 143)	p*
Gender (girls/boys)	245 (61.3%)/155 (38.8%)	161 (62.6%)/96 (37.4%)	84 (58.7%)/59 (41.3%)	0.442
Age at closure (years)	3.0 (0.1–17.8)	3.5 (0.3–17.5)	2.5 (0.1–15.7)	<0.001
Weight at closure (kg)	14.5 (3.5–110)	15.1 (4.8–110.0)	12.4 (3.5–67.0)	<0.001
ASD size (mm)	13.0 (4.1–37.0)	12.0 (4.1–30.0)	13.5 (5.0–37.0)	0.042
ASD-to-weight ratio	0.9 (0.1–4.3)	0.8 (0.1–2.5)	1.1 (0.2–4.3)	<0.001
Gestational age at birth (weeks)	38.5 (22.0–44.0)	39.0 (23.0–43.0)	38.0 (22.0–44.0)	0.758
Additional CHD	111 (27.8%)	60 (23.3%)	51 (35.7%)	0.008
Chromosomal defect	45 (11.3%)	29 (11.3%)	16 (11.2%)	0.977
Preterm (<37 weeks)	87 (21.8%)	56 (21.8%)	31 (21.7%)	0.979
Late premature (32 to <37 weeks)	59 (14.8%)	41 (16.0%)	18 (12.6%)	0.363
Very premature (28 to <32 weeks)	13 (3.3%)	8 (3.1%)	5 (3.5%)	0.836
Extreme premature (<28 weeks)	15 (3.8%)	7 (2.7%)	8 (5.6%)	0.148
Arrhythmias prior to ASD closure	15 (3.8%)	8 (3.2%)	7 (4.9%)	0.390
Pulmonary disease	45 (11.3%)	30 (11.7%)	15 (10.6%)	0.737
IRDS	24 (6.0%)	16 (6.2%)	8 (5.6%)	0.799
BPD	17 (4.3%)	10 (3.9%)	7 (4.9%)	0.633
Neonatal respiratory ventilation	21 (5.3%)	11 (4.3%)	10 (7.0%)	0.215
Neonatal CPAP	47 (11.8%)	27 (10.5%)	20 (14.0%)	0.307
Neonatal sepsis	24 (6.0%)	15 (5.8%)	9 (6.3%)	0.840
Pulmonary Hypertension	33 (8.3%)	19 (7.4%)	14 (9.8%)	0.410
Symptomatic ASD	47 (11.8%)	19 (7.4%)	28 (19.6%)	<0.001

ASD = atrial septal defect; BPD = bronchopulmonary dysplasia; CHD = congenital heart defects; CPAP = continuous positive airway pressure; IRDS = infant respiratory distress syndrome.
*Comparing percutaneous device closure with surgery.

was associated with major events in univariate conditional regression analyses (Table 5).

Associations between risk factors and adverse events. Multivariate adjusted regression model

Neither premature birth, as a group or by gestational sub-groups, pulmonary diseases, general ventilatory support nor neonatal sepsis were associated with major events following atrial septal defect closure after adjusting for potential confounding factors (Table 6). Symptomatic atrial septal defects were associated with both major adverse events (OR = 2.80 CI 95% 1.23–6.37) and minor adverse events (OR = 2.18 CI 95% 1.05–8.06) following all types of atrial septal defect closure and adjusted for confounding factors. Among children with surgical atrial septal defect closure, symptomatic atrial septal defects were associated with major adverse events (OR = 4.50 CI 95% 1.47–13.80), taking into account potential confounding factors (Table 6).

Discussion

This is one of the first studies assessing neonatal risk factors' association to adverse events after atrial septal defect closure. Some risk factors such as neonatal respiratory support as well as presence of pulmonary hypertension, additional congenital heart defects, pulmonary disease, and symptomatic atrial septal defects were associated with major adverse events following atrial septal defect closure in the univariate analyses. However, in the multivariate analysis, adjusted for potential confounding risk factors, this association was only present among children with symptomatic atrial septal defects. Hence, few or none of the neonatal factors seem to be associated with adverse events after atrial septal defect closure. Though preterm children are a heterogeneous group with multifactorial morbidity, our results are encouraging and an early indicated necessitous atrial septal defect closure can be regarded as safe in these children.

Few studies have previously described adverse events in small children after atrial septal defect closure.[24,25] These studies have assessed several risk factors but have not included neonatal factors and comorbidities associated with preterm birth.[26–28] The combination of cardiac alterations and neonatal morbidity may have an aggravating synergistic effect and potentially contribute to an increased risk of adverse events after atrial septal defect closure.[11,12]

It is well known that there are technical difficulties inherent in percutaneous device closure in smaller children, and thus surgical closure might have been the choice of preference in smaller children in our study. Further, a larger atrial septal defect-to-weight ratio is a known risk factor associated with adverse events in surgical closure.[25,29] Our study supports these findings, as children with major events following all atrial septal defect closure were lighter, younger, and had a larger atrial septal defect-to-weight ratio compared to controls.

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Table 3. Risk factors following all types of ASD closure

Risk factors associated with adverse events following all types of ASD closure. Univariate analysis.								
	Cases (major events) (n = 49)	Control (No major events)	p χ^2	OR (CI 95%)	Cases (minor events) (n = 87)	Control (No minor events)	p χ^2	OR (CI 95%)
Gender (girls/boys)	33 (73.3%)/12(26.7%)	206 (59.0%)/143(31.0%)	0.176	0.58 (0.30–1.11)	48 (55.8%)/38(44.2%)	197 (62.9%)/116(37.1%)	0.261	1.32 (0.82–2.12)
Age at closure (years)	1.8 (0.1–16.8)	3.2 (0.3–17.8)	0.008		2.4 (0.4–17.8)	3.2 (0.1–17.4)	0.321	
Weight at closure (kg)	11.0 (3.5–64.2)	14.6 (4.5–110)	0.007		12.6 (4.5–79.0)	14.6 (3.5–110.0)	0.333	
ASD size (mm)	13 (5.0.37.0)	12.3 (4.0–30.0)	0.778		14.0 (5.0–37.0)	12.0 (4.1-31.0)	0.065	
ASD-to-weight ratio	1.1 (0.3–2.7)	0.8 (0.1–4.3)	0.008		1.0 (0.1–4.3)	0.8 (0.1–3.0)	0.153	
Gestational age (weeks)	38.0 (22.0–44.0)	39.0 (23.0–23.0)	0.067		38.0 (23.0–42.0)	39.0 (22.0–43.0)	0.765	
Additional CHD	19 (42.2%)	89 (25.5%)	0.018	2.20 (1.20–4.08)	27 (32.9%)	81 (26%)	0.208	1.43 (0.86–2.39)
Chromosomal defects	5 (11.1%)	38 (10.9%)	0.964	1.37 (0.58–3.27)	12 (14.6%)	31 (9.9%)	0.225	1.53 (0.77–3.09)
Preterm	11 (24.4%)	76 (21.8%)	0.685	1.04 (0.51–2.14)	19 (23.2%)	68 (21.8%)	0.789	1.00 (0.57–1.79)
Late premature	4 (8.9%)	55 (15.8%)	0.197	0.49 (0.17–1.38)	11 (13.4%)	48 (15.4%)	0.656	0.80 (0.40–1.61)
Very premature	3 (6.7%)	10 (2.9%)	0.227	2.22 (0.60–3.27)	3 (3.7%)	10 (3.2%)	0.840	1.08 (0.29–4.02)
Extreme premature	4 (8.9%)	11 (3.2%)	0.096	2.74 (0.84–9.00)	5 (6.1%)	10 (3.2%)	0.250	1.85 (0.61–5.56)
Pulmonary disease	10 (22.2%)	34 (9.8%)	0.013	2.38 (1.09–5.20)	9 (11.0%)	35 (11.3%)	0.943	0.91 (0.42–1.98)
IRDS	6 (13.3%)	19 (5.5%)	0.042	2.43 (0.92–6.42)	5 (6.1%)	20 (6.4%)	0.912	0.89 (0.32–2.45)
BPD	4 (8.9%)	13 (3.7%)	0.151	2.30 (0.72–7.37)	3 (3.7%)	14 (4.5%)	0.736	0.76 (0.21–2.71)
Neonatal respiratory ventilation	8 (17.8%)	13 (3.7%)	<0.001	5.04 (1.97–12.90)	16 (5.2%)	5 (6.1%)	0.738	1.12 (0.47–3.15)
Neonatal CPAP	12 (26.7%)	35 (10.1%)	<0.001	2.92 (1.39–6.11)	13 (15.9%)	34 (10.9%)	0.222	1.44 (0.745–3.57)
Neonatal sepsis	6 (13.3%)	18 (5.2%)	0.031	2.57 (0.97–6.84)	6 (7.3%)	18 (5.8%)	0.607	1.21 (0.47–2.86)
Pulmonary Hypertension	8 (17.8%)	24 (6.9%)	0.012	3.06 (1.33–7.03)	10 (12.2%)	22 (7.1%)	0.131	1.63 (0.745–3.57)
Symptomatic ASD	13 (28.9%)	33 (9.5%)	<0.001	3.86 (1.88–7.89)	17 (20.7%)	29 (9.3%)	0.004	2.29 (1.20–4.39)

ASD = atrial septal defect; BPD = bronchopulmonary dysplasia; CHD = congenital heart defects; CPAP = continuous positive airway pressure; IRDS = infant respiratory distress syndrome.

Table 4. Risk factors following ASD surgical repair

Risk factors associated with adverse events following ASD *surgical* repair. Univariate analysis.								
	Cases (major events) (n = 32)	Control (No major events)	p χ^2	OR (CI 95%)	Cases (minor events) (n = 65)	Control (No minor events)	p χ^2	OR (CI 95%)
Gender (girls/boys)	23 (71.9%)/9(28.1%)	61 (55.5%)/49(44.5%)	0.096	0.55 (0.24–1.28)	35 (54.7%)/29(45.3%)	49 (62.8%)/29(37.2%)	0.327	1.37 (0.70–2.67)
Age at closure (years)	1.5 (0.1–15.7)	2.7 (0.4–13.6)	0.206		2.1 (0.4–15.7)	2.7 (0.1–13.2)	0.770	
Weight at closure (kg)	9.2 (3.5–61.5	12.6 (4.5–67.0)	0.122		12.3 (4.5–67.0)	12.5 (3.5–53.0)	0.652	
ASD size (mm)	14.0 (5.0–37.0)	13.0 (6.0–28.0)	0.855		14.0 (5.0–37.0)	13.0 (6.0–31.0)	0.687	
ASD-to-weight ratio	1.1 (0.3–2.7)	1.0 (0.2–4.3)	0.335		1.0 (0.2–4.3)	1.1 (0.4–3.0)	0.833	
Gestational age (weeks)	38.0 (22.0–44.0)	39.0 (23.0–42.0)	0.177		38.0 (22.0–42.0)	39.0 (23.0–42.0)	0.756	
Additional CHD	16 (53.3%)	34 (30.9%)	0.023	2.27 (1.02–5.05)	23 (36.5%)	27 (35.1%)	0.859	1.03 (0.52–2.06)
Chromosomal defects	4 (13.3%)	11 (10%)	6.01	1.68 (0.54–5.26)	10 (15.9%)	5 (6.5%)	0.074	2.18 (0.75–6.37)
Preterm	6 (20.0%)	25 (22.7%)	0.750	0.79 (0.29–2.14)	14 (22.2%)	17 (22.1%)	0.984	0.97 (0.44–2.19)
Late premature	0 (0.0%)	18 (16.4%)	0.013	–	8 (12.7%)	10 (13.0%)	0.960	0.95 (0.35–2.58)
Very premature	2 (6.7%)	3 (2.7%)	0.291	2.40 (0.38–15.03)	3 (4.8%)	2 (2.6%)	0.657	1.84 (0.30–11.35)
Extreme premature	4 (13.3%)	4 (3.6%)	0.065	3.62 (0.90–16.24)	3 (4.8%)	5 (6.5%)	0.730	0.70 (0.16–3.08)
Pulmonary disease	8 (26.7%)	7 (6.4%)	0.002	4.90 (1.62.14.84)	6 (9.5%)	9 (11.8%)	0.661	0.77 (0.26–2.29)
IRDS	4 (13.3%)	4 (3.7%)	0.066	3.78 (0.90–16.09)	3 (4.8%)	5 (6.6%)	0.729	0.70 (0.16–3.03)
BPD	4 (13.3%)	3 (2.8%)	0.039	5.10 (1.07–24.10)	2 (3.2%)	5 (6.6%)	0.456	0.46 (0.09–4.04)
Neonatal respiratory ventilation	5 (16.7%)	5 (4.5%)	0.022	3.93 (1.06–14.55)	4 (6.3%)	6 (7.8%)	1.00	0.79 (0.21–2.92)
Neonatal CPAP	8 (26.7%)	12 (10.9%)	0.029	2.75 (1.01–7.47)	11 (17.5%)	9 (11.7%)	0.332	1.56 (0.60–4.04)
Neonatal sepsis	4 (13.3%)	5 (4.6%)	0.101	3.00 (0.76–11.62)	3 (4.8%)	6 (7.9%)	0.455	0.54 (0.14–2.39)
Pulmonary hypertension	7 (23.3%)	6 (5.5%)	0.003	5.83 (1.81–18.38)	8 (12.7%)	5 (6.5%)	0.208	1.68 (0.55–2.87)
Symptomatic ASD	13 (43.3%)	14 (12.7%)	<0.001	5.39 (2.20–13.19)	14 (22.2%)	13 (16.9%)	0.426	1.26 (0.55–2.87)

ASD = atrial septal defect; BPD = bronchopulmonary dysplasia; CHD = congenital heart defects; CPAP = continuous positive airway pressure; IRDS = infant respiratory distress syndrome.

Table 5. Risk factors following all types of percutaneous device ASD closure

Risk factors associated with adverse events following *percutaneous device* ASD closure. Univariate analysis.								
	Cases (major events) (n = 17)	Control (No major events)	p χ^2	OR (CI 95%)	Cases (minor events) (n = 22)	Control (No minor events)	p χ^2	OR (CI 95%)
Gender (girls/boys)	13 (76.5%)/4(23.5%)	148 (61.6%)/92(38.4%)	0.302	0.49 (0.16–1.52)	13 (59.0%)/9(41.0%)	148 (62.9%)/87(37.1%)	0.718	1.13 (0.47–2.71)
Age at closure (years)	3.2 (0.4–16.8)	3.6 (0.3–17.8)	0.075		4.2 (0.5–17.8)	3.5 (0.3–17.4)	0.375	
Weight at closure (kg)	11.5 (4.8–64.3)	15.2 (5.1–110.0)	0.122		17.1 (5.6–79.4)	15.1 (4.8–110)	0.457	
ASD size (mm)	12.0 (6.0–24.0)	12.0 (4.1–30.0)	0.621		14.0 (7.0–30.0)	12.0 (4.1–27.0)	0.192	
ASD-to-weight ratio	1.0 (0.3–1.7)	0.8 (0.1–2.5)	0.157		0.6 (0.1–2.5)	0.8 (0.1–2.4)	0.365	
Gestational age (weeks)	38.0 (28.0–42.0)	39.0 (23.0–43.0)	0.243		38.0 (24.0–41.0)	39.0 (23.0–43.0)	0.463	
Additional CHD	3 (21.4%)	55 (23.0%)	0.891	1.40 (0.47–4.15)	4 (22.2%)	54 (23.0%)	1.00	1.26 (0.47–3.37)
Chromosomal defects	1 (7.1%)	27 (11.3%)	1.00	1.05 (0.23–4.85)	2 (11.1%)	26 (11.1%)	0.630	1.27 (0.35–4.58)
Preterm	5 (35.7%)	51 (21.3%)	0.208	1.54 (0.52–5.58)	5 (27.8%)	51 (21.7%)	0.550	1.06 (0.37–3.02)
Late premature	4 (28.6%)	37 (15.5%)	0.196	1.69 (0.52–5.46)	3 (16.7%)	38 (16.2%)	0.956	0.82 (0.23–2.90)
Very premature	1 (7.1%)	7 (2.9%)	0.370	2.08 (0.24–17.69)	0 (0.0%)	8 (3.4%)	–	–
Extreme premature	0 (0.0%)	7 (2.9%)	–	–	2 (11.1%)	5 (2.1%)	0.081	4.60 (0.83–25.24)
Pulmonary disease	2 (14.3)	27 (11.3%)	0.733	1.05 (0.23–4.85)	3 (16.7%)	26 (11.1%)	0.443	1.27 (0.35–4.63)
IRDS	2 (14.3%)	15 (6.3%)	0.240	2.00 (0.42–9.57)	2 (11.1%)	15 (6.4%)	0.345	1.47 (0.31–6.88)
BPD	0 (0.0%)	10 (4.2%)	–	–	1 (5.6%)	9 (3.8%)	0.529	1.20 (0.14–9.90)
Neonatal respiratory ventilation	2 (31.4%)	8 (3.4%)	0.018	6.16 (1.47–25.80)	1 (5.6%)	10 (4.3%)	0.567	1.06 (0.13–8.70)
Neonatal CPAP	4 (28.9%)	23 (9.7%)	0.050	2.89 (0.87–9.60)	2 (11.1%)	25 (10.7%)	1.00	0.84 (0.18–3.79)
Neonatal sepsis	2 (14.3%)	13 (5.4%)	0.197	2.33 (0.48–11.28)	3 (16.7%)	12 (5.1%)	0.080	2.93 (0.76–11.31)
Pulmonary hypertension	1 (7.1%)	18 (7.6%)	1.00	0.77 (0.10–6.12)	2 (11.1%)	17 (7.3%)	0.663	1.13 (0.28–5.62)
Symptomatic ASD	0 (0.0%)	19 (7.9%)	–	–	3 (16.7%)	16 (6.8%)	0.145	2.16 (0.59–8.08)

ASD = atrial septal defect; BPD = bronchopulmonary dysplasia; CHD = congenital heart defects; CPAP = continuous positive airway pressure; IRDS = infant respiratory distress syndrome.

Table 6. Adjusted risk factors

Adjusted risk factors for adverse events						
	All types of ASD closure		Percutaneous device closure		Surgery	
	OR major events	OR minor events	OR major events	OR minor events	OR major events	OR minor events
Preterm >32 to <37 gestational age	0.35 (0.10–1.18)	0.80 (0.37–1.76)	1.07 (0.27–4.27)	0.92 (0.23–3.70)	–	0.78 (0.25–2.42)
Preterm <32 weeks of gestational age	0.69 (0.18–2.68)	1.23 (0.34–4.45)	0.75 (0.06–9.98)	1.43 (0.14–15.11)	0.59 (0.03–12.66)	1.48 (0.16–13.34)
Pulmonary diseases and general ventilatory support	2.51 (0.83–7.64)	1.04 (0.41–2.67)	2.17 (0.46–10.15)	0.53 (0.08–3.58)	3.82 (0.28–52.00)	1.45 (0.34–6.15)
Neonatal sepsis	1.20 (0.34–4.31)	0.77 (0.24–2.48)	2.78 (0.48–16.22)	3.10 (0.60–15.92)	0.56 (0.07–4.54)	0.25 (0.03–1.88)
Pulmonary hypertension	1.32 (0.48–3.59)	1.07 (0.43–2.68)	0.75 (0.07–8.06)	0.81 (0.14–4.86)	2.50 (0.52–12.03)	1.71 (0.43–6.82)
Symptomatic ASD	2.80 (1.23–6.37)	2.18 (1.05–4.52)	–	1.19 (0.39––8.42)	4.50 (1.47–13.80)	1.05 (0.39–2.80)

ASD = atrial septal defect.

Preterm birth, regardless of gestational age group, was not associated with an increased risk of major adverse events following atrial septal defect closure.

Additional congenital heart defects, neonatal respiratory support, pulmonary comorbidity, and neonatal sepsis often have to be taken into consideration in the care of the preterm child. These factors were more common among cases with major events following atrial septal defect closure, but did not reach significance as risk factors in the adjusted model. Furthermore, the prematurely born children may suffer from reduced right ventricular function, altered pulmonary capillary bed maturation, and sub-clinical pulmonary hypertension.[10,12,30,31] All this combined may contribute to an increased risk of symptoms of atrial septal defect as well as adverse events following closure. None of the above risk factors, except for symptomatic atrial septal defects, were independently associated with adverse events after atrial septal defect closure when adjusted for potential confounding factors. This indicates that the altered morphological, global structural differences and functional impairment of the preterm child's heart does not influence the risk of adverse events after atrial septal defect closure.[10–13] Premature children with severe pulmonary comorbidity may however benefit from early atrial septal defect closure as has been suggested previously.[14,32] Further studies identifying benefits of early atrial septal defect closure in this group of new survivors are needed.

Symptomatic atrial septal defects or clinically manifested heart failure has been reported to be present in 11.6–20% of children with atrial septal defect and even more common in children with large atrial septal defects.[33,34] This is in line with our study, as 48 (12%) of the children had symptomatic atrial septal defects. This rules out the risk of selection bias due to overtreatment in our study. Children with symptomatic atrial septal defects were almost three times as common among children with major events (28.9 vs. 9.5%) and twice as common among children with minor events (20.7 vs. 9.8%) compared to controls in our study. Even after adjusting for potential confounding factors, the risk of major adverse events was almost three times as high and minor events twice as high in children with symptomatic atrial septal defects. This indicates that children with symptomatic atrial septal defects may carry a more severe morbidity compared to children with no symptoms. The bias for selection to surgical repair might be in favour for children with severe atrial septal defect morbidity, which in turn may increase the risk of major events in the surgical cases even after adjusting for all other factors.[25,29] For complex and large atrial septal defect, surgical repair is still considered the most favourable method with long-term favourable outcomes.[35]

Significant arrhythmias occurred in 11 (22.9%) of all children in our study. This was more common among children with symptomatic atrial septal defects. Symptomatic atrial septal defects, often with an enlarged right ventricle caused by volume overload, may induce the same trigger to arrhythmias in cases of atrial septal defect closure as in other congenital heart defects such as tetralogy of Fallot.[36] Thus, to decrease the risk of arrhythmias, these children might benefit from an early atrial septal defect closure.

This study is limited by the retrospective design, which may increase the risk of selection and recall bias. However, we believe that the risk of missing data due to incomplete registration in medical records and national registers is limited as we used both sources to retrieve demographic data, potential risk and confounding factors, and information on adverse events. Recent validation studies of the two registries in our study have found good coherence between the medical records and registries.[37,38] Further, the number of included cases and controls in our study is substantial, which often increases the power in the conditional logistic analyses. However, since our study had cases with few adverse events, a risk of non-robust models was present.[39] Thus, to reduce this risk, we grouped the similar potential synergistic factors in a second model of analysis (Table 1). The adjusted risk of adverse events within one year after atrial septal defect closure did not alter in the second model.

In our study, we obtained data from two of the Swedish paediatric cardiac centres, performing two-thirds of all percutaneous device closure and half of all paediatric heart surgeries, according to the 2017 annual rapport from the Swedish Registry of Congenital Heart Disease.[40] One of the two interventional centres refers patients for surgery to the other centre. By this approach, a harmonisation concerning indications and choice of interventional method (surgery or percutaneous) is made and reduces the risk of selection biased due to method in this study.

Conclusion

Neonatal comorbidities were not associated with increased risk of major and minor adverse events after atrial septal defect closure. Children with neonatal pulmonary morbidity may be a selected group suffering from right-ventricular function impairment and reduced pulmonary capillary bed maturation, and a careful assessment and risk stratification can be advised in this group.

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Children with symptomatic atrial septal defects have a two to four times increased risk of major events, predominantly peri-interventional arrhythmias, during or following an atrial septal defect closure, suggesting that a post-interventional follow-up with regard to arrhythmias should be considered in this group.

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Conflict of Interests. None.

Ethical Standards. The authors assure that all procedures contributing to this work is in adherence with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

This study was approved by the Ethics Committee for Human Research at Umeå University (D-nr 2015-10-31M allteration 2015-88-32M), and informed consent was optained by everyone in the study population or each guardian of the included children.

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