The association between congenital heart disease and small for gestational age with regard to the prevalence and outcomes

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Complete List of Authors:	Ishikawa, Takamichi; Hamamatsu University School of Medicin, Paediatrics Uchiyama, Hiroki; Hamamatsu University School of Medicin, Paediatrics Baba, Toru; Hamamatsu University School of Medicin, Paediatrics Ohishi, Akira; Hamamatsu University School of Medicin, Paediatrics Iijima, Shigeo; Hamamatsu University School of Medicin, Paediatrics Iwashima, Satoru; Hamamatsu University School of Medicin, Paediatrics
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The association between congenital heart disease and small for gestational age with regard to the prevalence and outcomes

Takamichi Ishikawa, MD, PhD; Hiroki Uchiyama, MD; Toru Baba, MD; Akira Ohishi, MD, PhD; Shigeo Iijima, MD, PhD; Satoru Iwashima, MD, PhD

Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan

Short title: Congenital heart disease and small for gestational age

Corresponding author: Takamichi Ishikawa, MD, PhD, Department of Pediatrics, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan

Tel: +81-053-435-2312, fax: +81-053-435-2311, e-mail: ishikawa@hama-med.ac.jp

Abstract

Aim: To evaluate the association between small for gestational age (SGA) and the prevalence of congenital heart disease (CHD) and the association of the SGA status with the outcomes among infants with CHD.

Methods: Echocardiography was performed within the first 5 days of life in 5664 consecutive infants. Infants were classified into four groups according to the presence or absence of SGA and CHD. All CHD infants were followed up until either spontaneous resolution of all cardiac lesions, invasive intervention, or death. All newborns without CHD were followed for mortality until the final follow-up date.

Results: A total of 303 infants were diagnosed with CHD, while 610 were diagnosed with SGA. Among the CHD infants, 56 were SGA, and 247 were not. A multivariable logistic regression analysis showed that the adjusted odds ratio of SGA (9.71, $p<0.001$) was significantly higher than that of other parameters concerning predictors of invasive intervention or death. The mortality rate in the presence of both SGA and CHD (hazard ratio: 33.6, $p<0.001$) was markedly higher than in the absence of both.

Conclusion: SGA was a significant predictor of invasive intervention for CHD. The combination of CHD and SGA carried a high risk of death beyond that of either alone.

Key words: Congenital heart disease, Infants, Small for gestational age

Key Notes:

- Little is known about the association between congenital heart disease (CHD) and small for gestational age (SGA) and its effect on infants' outcomes in a large-scale study.
- We evaluated the association between SGA and prevalence of CHD and the association of SGA status with outcomes among infants with CHD.
- The combination of CHD and SGA carried a high risk of death beyond that of CHD or SGA alone.

Introduction

Congenital heart disease (CHD) is the most prevalent birth defect and frequently requires multiple hospitalizations and surgical procedures. Many of these infants require corrective or palliative surgery and extensive hospitalization during early life (1). To improve morbidity and mortality associated with CHD in the infantile period, identifying and stratifying those at highest risk are required. Small for gestational age (SGA) is clearly associated with CHD. SGA is a significant preoperative risk factor for morbidity and mortality in infants with CHD undergoing cardiothoracic surgery (2, 3). Infants who are SGA may have a constitutional reduction in their growth or may have intrauterine growth restriction due to a pathological process (environmental, maternal health, placental abnormality, or a primary etiology with the fetus). Limitations of fetal growth may affect developmental pathways within the cardiovascular system or other organs, which can have life-long effects.

Although infants born with CHD are twice as likely to be SGA as those born without CHD (4), little is known about the prevalence of CHD in infants with SGA. Most previous studies retrospectively assessed the postoperative outcomes for SGA with CHD in small-scale case-control studies (2, 3). Therefore, prospective studies

on the association between CHD and SGA, as well as on the outcomes of a large number of infants, are necessary. Furthermore, no prospective cohort studies have performed echocardiographic screening of a large number of consecutive infants.

Therefore, this study aimed to evaluate the association between CHD and SGA in relation to the prevalence of CHD and outcomes of consecutive infants.

Methods

Study population

This prospective cohort study was carried out at Hamamatsu University Hospital, Japan. Echocardiography was performed in consecutive live-born neonates between May 2005 and November 2016. Echocardiographic examinations were performed within 5 days old (mean ± standard deviation [SD]: 1.7±0.8 days old). Infants were classified into 4 groups according to the presence or absence of SGA and CHD as follows: (1) not SGA without CHD (reference group), (2) not SGA with CHD, (3) SGA without CHD, and (4) SGA with CHD. All infants were followed up for mortality outcomes using the hospital case detection system until the final follow-up date (30 June 2018). All infants with CHD were followed up by echocardiography

until either spontaneous resolution of all cardiac lesions occurred, they received invasive intervention (surgery or catheter intervention), or they died. Infants without CHD were followed up using a child health checkup system.

The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki and was approved by local ethics committee. Written informed consent was obtained from the parents of each newborn.

Echocardiography

Echocardiographic examinations were performed with either a Toshiba Nemio 30 (Toshiba Medical Systems Inc., Tokyo, Japan), PHILIPS HD11XE (Philips Medical Systems, Andover, MA, USA), or Vivid q (GE Medical Systems, Milwaukee, WI, USA) with an 8- or 12-MHz transducer. The examination protocol included 2-dimensional and color Doppler imaging from the parasternal, suprasternal, subxiphoid, apical, and (when necessary) modified views. To avoid false-positive signals, color flow mapping was performed using the appropriate gain and filter settings (5, 6). Each echocardiographic examination was performed by 1 of 3 pediatric cardiologists (T.I., K.S., S.I.). All examinations were recorded and

reviewed by another pediatric cardiologist who was blinded to the patient's identity. Sedation was not required for any infants because echocardiographic screening was performed during natural sleep.

Definitions of CHD

CHD was defined as gross structural abnormality of the heart, or intrathoracic great vessels with functional significance or with the potential to be significant (7). Considering that patent ductus arteriosus (PDA) was common in children with CHD, infants with PDA were selected only if they were born at >37 weeks of gestational age and the PDA did not close spontaneously within the first month of life (8). Atrial septal defect was defined as the presence of an intra-atrial communication ≥4 mm in diameter, with an enlarged right atrium and ventricle. An intra-atrial defect <4 mm in size at the fossa ovalis was considered to represent a patent foramen ovale (9, 10). The types of ventricular septal defect (VSD) were defined and classified as previously described. (11). A subset of severe CHDs was defined according to previous studies, and included atrioventricular canal defects, truncus arteriosus communis (TAC), total anomalous pulmonary venous return, tetralogy of Fallot

(TOF), pulmonary atresia, tricuspid atresia, hypoplastic left heart syndrome (HLHS), Ebstein anomaly, aortic stenosis (AS), transposition of the great arteries (TGA), coarctation of the aorta (CoA), double outlet right ventricle (DORV), and interrupted aortic arch (IAA) (12, 13). Arrhythmias unassociated with structural malformations were also excluded (7).

Definitions of SGA, chromosomal abnormalities, and extracardiac anomalies

SGA was defined as a birth weight <10th percentile for gestational age and sex based on the standardized birth weight distribution of live births in Japan (14, 15).

We analyzed chromosomes by GTG-banding in all patients suspected of chromosomal abnormalities. When required, 2 or 3 banding techniques were combined. We then performed microdeletion analysis using fluorescence *in situ* hybridization when conventional chromosomal analysis showed a normal karyotype. Notably, the decision to perform cytogenetic testing was at the discretion of the health care providers caring for the newborns based on clinical suspicion. Therefore, not all newborns were tested.

We chose to focus on major anomalies based on previous definitions for

congenital extracardiac anomalies. (16, 17).

Statistical analyses

Data are presented as the mean (SD) or median (interquartile range). For comparison among the groups, a one-way ANOVA and Tukey's test were used for parametric variables, and the Kruskal–Wallis test with post hoc comparison by Dunn's multiple comparison test was used for nonparametric variables. The χ^2 test or Fisher's exact test was used for categorical variables. Kaplan–Meier survival curves were estimated and differences between groups were assessed by the log-rank test, using the day of birth as time zero. We performed multivariable logistic regression analysis for evaluating predictors of surgery or catheter intervention and death in newborns with CHD. Univariate analysis for each variable was conducted, followed by multivariate analysis, (using $p<0.05$ from univariate analysis). Event-free survival was defined as the time from birth to the date of surgical repair or catheter intervention for cardiac lesions, death (due to any cause), or the latest follow-up. Multivariable Cox proportional hazards regression analysis was performed to identify factors independently associated with event-free survival. Statistical significance was

defined as $p<0.05$. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

Of the 5664 infants born alive during the study period, 610 (10.8%) had SGA and 5054 (89.2%) did not. Among the infants with SGA, 56 (9.2%) were diagnosed with CHD (SGA with CHD) and 554 (90.8%) were not (SGA without CHD). Among the infants without SGA, 247 (4.9%) were diagnosed with CHD (not SGA with CHD) and 4807 (95.1%) were not (not SGA without CHD). A total of 303 infants were diagnosed with CHD, and the overall prevalence of CHD in the study population was 53.4 per 1000 live births. The prevalence of SGA in infants with CHD was significantly higher than that in those without CHD (184.8 vs. 103.3 per 1000 live births, odds ratio [OR]: 1.97, 95% confidence interval [CI]: 1.45-2.66, $p<0.001$) (**Figure 1**).

Clinical characteristics of the study group are shown in Table 1. Infants with SGA and CHD had a younger gestational age ($p<0.05$), higher rate of preterm birth (gestational age <37 weeks) ($p<0.01$), lower birth weight ($p<0.001$), higher rate of

low-birth-weight infants (birth weight <2500 g) ($p<0.05$), and lower Apgar scores at 1 ($p<0.01$) and 5 ($p<0.01$) min than those in the other groups. The rates of extracardiac anomalies ($p<0.05$) and chromosomal abnormalities ($p<0.001$) in infants with SGA and CHD were significantly higher than those in the other groups.

VSD (n=165, 54.4%) was the most frequent cardiac abnormality in infants with CHD. Among infants with VSD, 4 (2.4%) had infundibular VSD, 62 (37.6%) had membranous VSD, and 99 (60.0%) had muscular VSD. The incidence of severe defects in newborns who were SGA was significantly higher than in those who were not SGA (21.4% vs. 6.9%, OR: 3.69, 95% CI: 1.65-8.26, $p<0.001$) (**Table 2**). Table 3 shows the predictors of severe CHD in infants with CHD. In a multivariable logistic regression analysis, the adjusted OR of SGA (7.01, 95% CI: 1.61-30.60) was significantly higher than that of other predictors of severe CHD ($p=0.010$).

Nineteen (33.9%) patients who were SGA with CHD and 27 (10.9%) who were not SGA with CHD underwent surgical repair or catheter intervention for cardiac lesions during the study period **(Figure 1)**. The 5-year event-free survival rate (57.9%) was significantly less in infants who were SGA with CHD than in those who were not SGA with CHD (89.5%, log-rank test, $p<0.001$) (**Figure 2**). Table 4

shows the predictors of surgery, catheter intervention, or death in infants with CHD. In multivariable logistic regression analysis, the adjusted OR of SGA (9.71, 95% CI: 2.87-32.85) was significantly higher than that of other parameters regarding a predictor of invasive intervention or death ($p<0.001$).

Overall, 14 infants died during a mean of 6.7±3.3 years of follow-up. Six infants (0.1%) who were not SGA without CHD, 1 (0.4%) who was not SGA with CHD, 3 (0.5%) who were SGA without CHD, and 4 (7.1%) who were SGA with CHD died **(Figure 1)**. The survival rate of infants who were SGA with CHD was significantly lower than that of those who were not SGA without CHD (log-rank test, $p<0.001$) (**Figure 3**). The overall mortality rate was 0.44 per 1000 person-years. Multivariable Cox proportional hazards regression analysis showed that the mortality rate was significantly higher in infants who were SGA with CHD (9.54 per 1000, hazard ratio: 33.6, 95% CI: 9.79-115.57, $p<0.001$) than in those who were not SGA without CHD (0.23 per 1000) **(Table 5)**.

Discussion

This study involved echocardiographic screening of a large number of consecutive

infants early after birth and we followed up these infants. The main findings of our cohort study were as follows: 1) infants with SGA were >3 times more likely to have severe CHD than those without SGA; 2) SGA was the most significant predictor of invasive intervention for CHD; and 3) the mortality rate was markedly higher in infants with SGA and CHD than in those with neither SGA nor CHD.

A previous case-control study showed a higher risk of SGA for each CHD subtype than with control subjects (4). In this previous study, the ORs of SGA in cases of left-sided obstructive defects (AS, HLHS, CoA, and IAA) and conotruncal defects (TGA, TOF, TAC, DORV, and IAA) were 1.83 and 2.41, respectively. In the present study, the rate of these defects (severe CHD) in infants with SGA was significantly higher than that in those without SGA. Other studies showed significant birth weight deficits in infants with severe VSD, which required surgery(18, 19). In this study, the rate of these infants with SGA (n=5; 11.4%) was significantly higher than that in those without SGA (n=7; 3.0%, p=0.028). These results indicate that infants with CHD and smaller birth weight are likely to have more complex and/or severe lesions, and are likely to require intervention. Moreover, the relative prevalence of severe CHDs was reported to be higher at earlier gestational ages than

at later gestational ages (20). In our study, gestational age was significantly younger in SGA infants with CHD than in those who were not SGA with CHD. Infants with fetal growth restriction are at risk for preterm delivery (21). Our findings suggested that SGA was closely related to severe CHDs.

The present study showed that event-free survival was significantly lower in infants with SGA and CHD than in those without SGA with CHD. Furthermore, SGA was more closely associated with the risk of surgery, catheter intervention, or death than with other parameters. In a previous study, 32.8% of infants with CHD underwent therapeutic procedures (surgery or catheter intervention), while 42.8% recovered spontaneously (22). This rate is similar to that in newborns with SGA and CHD in our study. However, in infants without SGA with CHD, the rate of surgery or catheter intervention was lower and that of spontaneous resolution was higher than the results of this previous study. Our study included many patients with mild defects who did not require therapeutic treatment. These patients might have been missed in previous studies because echocardiography was performed early after birth in our infants.

The mortality rate per 1000 person-years and hazard ratio were markedly

higher in infants with SGA and CHD than in the other groups. SGA is a risk factor for perinatal mortality and morbidity (23). A previous review showed that neonatal mortality among infants who were SGA was 3-fold higher than that in those who were appropriate for gestational age (24). Lin et al. found that neonatal mortality and morbidity rates were higher in SGA cases than in non-SGA cases because of fetal disorders, including chromosomal abnormalities and congenital malformations (25). The rates of chromosomal abnormalities in infants with SGA and CHD in the present study were significantly higher than those in the other groups. However, there was no significant difference in the mortality rate when infants with chromosomal abnormalities were excluded. Several previous studies that investigated postoperative outcomes in newborns with SGA and CHD, including patients with chromosomal abnormalities, reported that patients with SGA had a significantly higher mortality rate than those without SGA (2), while others reported no difference (3). In the present study, there was no difference in the postoperative discharge mortality rate between infants with SGA (10.5%) and those without SGA (0%). Our results indicate that the combination of CHD and SGA confers a high risk of death beyond that of CHD or SGA alone, which is strongly associated with chromosomal

abnormalities.

The prevalence of CHD in the present study was 53.4 per 1000 live births, and this amount is much higher than that in most previous studies (4-13 per 1000 live births) (7, 22, 26-28). However, Hoffman and Kaplan reported a high prevalence of CHD and estimated that CHD was diagnosed in approximately 50 neonates per 1000 live births if trivial lesions were included(12). Previous studies mainly documented the prevalence of CHD using surveillance registries. Because of echocardiographic screening early after birth in our study, a high number of patients with mild defects, such as muscular VSD or patent ductus arteriosus, which might have been missed in previous studies, may have been included. Our results probably represent the true prevalence of CHD.

We acknowledge several limitations of our study. First, there may have been some selection bias because all births occurred at one tertiary referral hospital. Second, not all fetuses that were SGA were pathologically growth restricted and in fact may have been constitutionally small. Similarly, not all fetuses that have not met their genetic growth potential are in less than the 10th percentile for estimated fetal weight. However, it was difficult to distinguish between these processes. Third,

decisions about cytogenetic testing were made by clinicians caring for the infants. Therefore, there is likely to have been large testing bias for those with CHD and SGA. Our results are likely to underestimate the true contribution of chromosomal abnormalities to CHDs. Fourth, while this study investigated a large number of infants, the mortality analysis was likely statistically underpowered and may not be generalizable because the total numbers of deaths and infants with SGA and CHD were small. Fifth, our data were limited to hospitalized events. Therefore out-of-hospital sudden cardiac death might only have been indirectly captured under all-cause mortality. Furthermore, not all subjects might have had the same time at risk because the last visit dates for not all subjects coincides with the final follow-up date. Finally, the numbers are too small to be able to statistically assess confounders and potential mediating effects, such as birth weight, gestational age, extracardiac anomalies, and chromosomal abnormalities. Further studies in a larger number of CHD infants with SGA are required.

Conclusions

SGA is a significant predictor of invasive intervention for CHD, and the combination

of CHD and SGA carries a high risk of death beyond that of CHD or SGA alone. For clinicians, especially the medical team taking care of these infants, our results provide important information for prognostication in terms of parental counseling as well as for making decisions about intervention.

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Conflicts of interest: The authors declare no conflicts of interest.

Abbreviations

CHD, congenital heart disease; SGA, small for gestational age; PDA, patent ductus arteriosus; VSD, ventricular septal defect; TAC, truncus arteriosus communis; TOF, tetralogy of Fallot; HLHS, hypoplastic left heart syndrome; AS, aortic stenosis; TGA, transposition of the great arteries; CoA, coarctation of the aorta; DORV, double outlet right ventricle; IAA, interrupted aortic arch; OR, odds ratio; CI, confidence interval

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Figure Legends

Figure 1. Flow diagram of the study population. SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; CHD, congenital heart disease.

Figure 2. Kaplan–Meier curves showing event-free survival for the combined endpoint of death, surgery, and catheter intervention in infants with CHD according to the presence of SGA. SGA, small for gestational age; CHD, congenital heart disease.

Figure 3. Kaplan–Meier cumulative estimates of the probability of surviving among the 4 groups. SGA, small for gestational age; CHD, congenital heart disease.

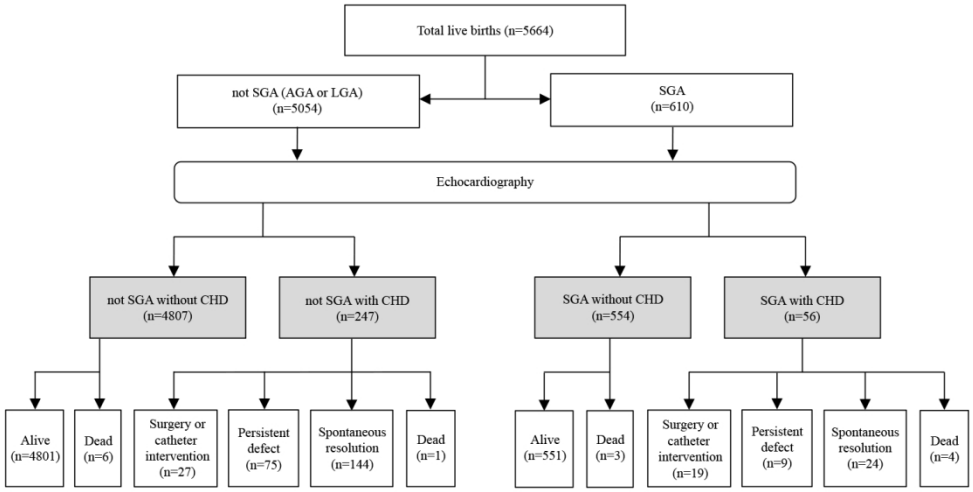

Total live births (n=5664)
not SGA (AGA or LGA) (n=5054)
SGA (n=610)
Echocardiography
not SGA without CHD (n=4807)
not SGA with CHD (n=247)
SGA without CHD (n=554)
SGA with CHD (n=56)
Alive (n=4801)
Dead (n=6)
Surgery or catheter intervention (n=27)
Persistent defect (n=75)
Spontaneous resolution (n=144)
Dead (n=1)
Alive (n=551)
Dead (n=3)
Surgery or catheter intervention (n=19)
Persistent defect (n=9)
Spontaneous resolution (n=24)
Dead (n=4)

Figure 1

Table 1. Clinical characteristics of the study group

	not SGA without CHD (n = 4807)	not SGA with CHD (n = 247)	SGA without CHD (n = 554)	SGA with CHD (n = 56)	P Value
Infant characteristics					
Male: Female	2475: 2332	102: 145	280: 274	24: 32	0.010
Gestational age (weeks)	38.4 ± 2.8	38.5 ± 1.6	37.6 ± 3.1	36.6 ± 3.3	<0.001
<37 weeks	740 (15.4%)	19 (7.7%)	132 (23.8%)	23 (41.1%)	<0.001
22-27 weeks	100	1	9	1	
28-31 weeks	114	0	18	5	
32-36 weeks	526	18	105	17	
Birth weight (g)	2893 ± 536	2984 ± 369	2176 ± 493	1938 ± 560	<0.001
<2,500 g	796 (16.6%)	10 (4.0%)	400 (72.2%)	49 (87.5%)	<0.001
Apgar score at 1 min	8.0 ± 1.5	8.1 ± 1.4	7.7 ± 1.8	6.6 ± 2.6	<0.001
Apgar score at 5 min	8.8 ± 1.2	8.9 ± 0.8	8.7 ± 1.4	7.9 ± 1.8	<0.001
Extracardiac anomaly	72 (1.5%)	11 (4.5%)	21 (3.8%)	8 (14.3%)	<0.001
Chromosomal abnormality	2 (0.04%)	14 (5.7%)	2 (0.4%)	14 (25.0%)	<0.001
Maternal characteristics					
Maternal age (years)	31.5 ± 5.0	31.6 ± 4.9	31.1 ± 5.3	32.7 ± 5.7	0.061
Caesarean delivery	1294 (26.9%)	55 (22.3%)	198 (35.7%)	31 (55.4%)	<0.001
Smoking during pregnancy	51 (1.1%)	5 (2.0%)	10 (1.8%)	2 (3.6%)	0.087
Drinking alcohol during pregnancy	97 (2.0%)	9 (3.6%)	16 (2.9%)	2 (3.6%)	0.182
Maternal CHD	40 (0.8%)	2 (0.8%)	2 (0.9%)	2 (3.6%)	0.082

SGA, small for gestational age; CHD, congenital heart disease

Values are presented as number, number (%), or mean ± standard deviation.

Table 2. Classification and numbers of patients with CHD

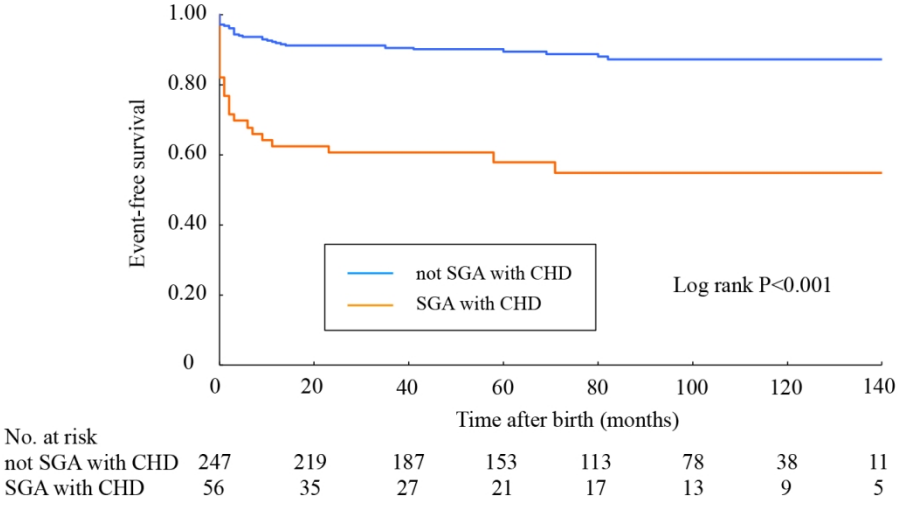
	not SGA with CHD	SGA with CHD	Total
Simple defects	230	44	274
VSD	138 (55.9%)	27 (48.2%)	165 (54.4%)
PDA	48 (19.4%)	6 (10.7%)	54 (17.8%)
ASD	16 (6.5%)	8 (14.2%)	24 (7.9%)
PS	12 (4.9%)	3 (5.4%)	15 (5.0%)
MVP	15 (6.1%)	0 (0%)	15 (5.0%)
BAV	1 (0.4%)	0 (0%)	1 (0.3%)
Severe defects	17	12	29
AVSD	1 (0.4%)	1 (1.8%)	5 (1.7%)
TOF	2 (0.8%)	1 (1.8%)	5 (1.7%)
DORV	1 (0.4%)	3 (5.4%)	4 (1.3%)
HLHS	1 (0.4%)	1 (1.8%)	3 (1.0%)
TGA	1 (0.4%)	1 (1.8%)	2 (0.7%)
CoA	1 (0.4%)	1 (1.8%)	2 (0.7%)
PA	1 (0.4%)	1 (1.8%)	2 (0.7%)
SV	1 (0.4%)	1 (1.8%)	2 (0.7%)
TAPVC	1 (0.4%)	1 (1.8%)	2 (0.7%)
TAC	0 (0%)	1 (1.8%)	1 (0.3%)
cAS	1 (0.4%)	0 (0%)	1 (0.3%)
Total	247 (100%)	56 (100%)	303 (100%)

CHD, congenital heart disease; VSD, ventricular septal defect; PDA, patent ductus arteriosus; ASD, atrial septal defect; PS, pulmonary stenosis; MVP, mitral valve prolapse; BAV, bicuspid aortic valve; AVSD, atrial ventricular septal defect; TOF, tetralogy of Fallot; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; CoA, coarctation of the aorta; PA, pulmonary atresia; SV, single ventricle; TAPVC, total anomalous pulmonary venous connection; TAC, truncus arteriosus communis; cAS, critical aortic stenosis.

Table 3. Predictors of severe CHD in infants with CHD

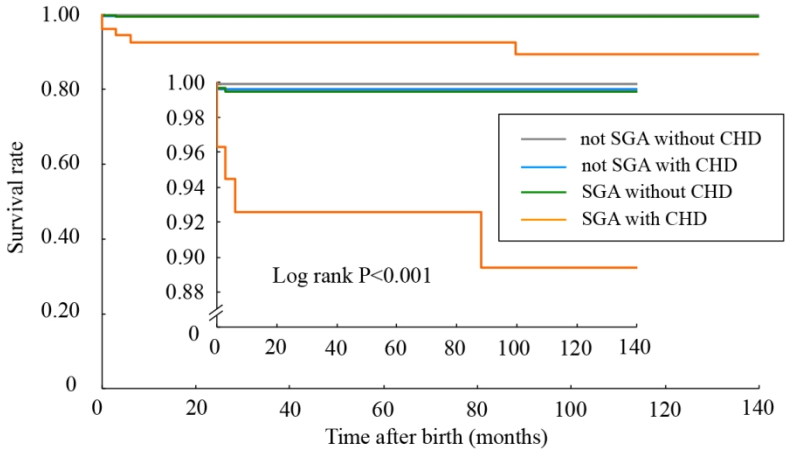
	Univariable Analysis			Multivariable Analysis		
	uOR	95% CI	P Value	aOR	95% CI	P Value
Sex	3.52	1.55 – 8.02	0.003			
Gestational week	1.04	0.86 – 1.25	0.710			
Birth weight	0.97	0.91 – 1.03	0.320			
Caesarean delivery	1.87	0.85 – 4.10	0.119			
Apgar score at 1 min	0.79	0.67 – 0.94	0.006			
Apgar score at 5 min	0.61	0.47 – 0.79	<0.001	0.46	0.23 – 0.93	0.029
Chromosomal abnormality	3.83	1.47 – 10.01	0.006	2.86	1.54 – 6.44	0.033
Extracardiac anomaly	5.24	1.82 – 15.07	0.002	4.61	1.33 – 16.02	0.016
SGA	3.69	1.65 – 8.26	0.002	7.01	1.61 – 30.60	0.010

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval; SGA, small for gestational age.



No. at risk								
not SGA with CHD	247	219	187	153	113	78	38	11
SGA with CHD	56	35	27	21	17	13	9	5

Figure 2



No. at risk								
not SGA without CHD	4807	4750	3564	2331	1228	279	140	36
not SGA with CHD	247	239	207	169	126	86	43	13
SGA without CHD	554	527	390	274	173	83	38	18
SGA with CHD	56	52	45	39	33	26	19	12

Figure 3

Table 4. Predictors of surgery, catheter intervention, or death in infants with CHD

	Univariable Analysis			Multivariable Analysis		
	uOR	95% CI	P Value	aOR	95% CI	P Value
Sex	2.20	1.20 – 4.04	0.011			
Gestational week	0.90	0.80 – 1.02	0.095			
Birth weight	0.93	0.89 – 0.98	0.003	1.14	1.03 – 1.25	0.011
Caesarean delivery	2.52	1.35 – 4.70	0.004			
Apgar score at 1 min	0.73	0.63 – 0.84	<0.001			
Apgar score at 5 min	0.52	0.40 – 0.67	<0.001			
Chromosomal abnormality	10.60	4.59 – 24.48	<0.001	5.86	2.04 – 16.85	0.001
Extracardiac anomaly	8.15	3.09 – 21.48	<0.001	7.24	2.26 – 23.20	0.001
SGA	5.87	3.03 – 11.34	<0.001	9.71	2.87 – 32.85	<0.001

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval; SGA, small for gestational age.

Table 5. Mortality rates (deaths per 1000 person-years) and HRs in relation to SGA and/or CHD

	Subjects	Deaths	Time at risk (Person-Years)	Mortality Rate per 1000 Person-Years	HR (95% CI)	P Value
not SGA without CHD	4807	6	26331	0.23	1.0 [Reference]	
not SGA with CHD	247	1	1657	0.60	2.0 (0.23 – 16.55)	0.528
SGA without CHD	554	3	2949	1.02	3.5 (0.87 – 13.88)	0.078
SGA with CHD	56	4	419	9.54	33.6 (9.79 – 115.57)	<0.001

CI, confidence interval; SGA, small for gestational age; CHD, congenital heart disease; HR, hazard ratio.