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Survival and Risk Factors for Mortality in Infants With Congenital Heart Disease in South Korea

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Abstract. *Background/Aim: The survival of patients with congenital heart disease (CHD) has dramatically improved over recent decades. However, a disparity exists depending on the country and medical system. This study aimed to analyze the survival of infants with CHD until the age of 18 years using large-scale population data in South Korea and investigate the effect of neonatal conditions at birth. Patients and Methods: We retrospectively extracted the Korean National Health Insurance Service claims data from January 2002 to December 2020. We included patients diagnosed with CHD who were less than one year of age. The follow-up duration was until their death or until they were censored before the age of 18 years. The CHD lesions were classified hierarchically (conotruncal, severe non-conotruncal, coarctation of the aorta, ventricular septal defect, atrial septal defect, and others). Several neonatal conditions were adopted as risk factors. Results: Overall, 127,958 infants had been diagnosed with CHD and 2,275 died before the age of 18 years. The survival rate of infants with CHD during childhood was 97.9%. The highest childhood mortality rate was associated with non-conotruncal defects (19.7%), followed by conotruncal defects (10.2%). The significant risk factors for childhood mortality were complex CHD, pulmonary hypertension, birth asphyxia, small for gestational age, respiratory distress, pulmonary hemorrhage, bronchopulmonary dysplasia, and convulsions. Conclusion: The survival of infants with CHD has been favorable in South Korea. Several neonatal conditions are risk factors for childhood mortality. Individualized risk assessment and optimal treatment strategies may help improve their survival rate.*

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Key Words: Congenital heart disease, infant, survival, risk factors.

Congenital heart disease (CHD) is among the most common congenital anomalies, occurring in approximately nine out of 1000 live births (1, 2). The survival rates of patients with CHD have dramatically improved over recent decades, driven by advances in treatment, including cardiac procedures and medical treatments (1, 2). Currently, more than 97% of CHD patients survive to adulthood (2). However, the mortality rate of patients with CHD is still higher than that of the general population (2, 3). Mortality in patients with CHD during childhood is the highest during infancy and decreases progressively thereafter (4, 5). In particular, CHD of greater severity correlated with a higher probability of death during infancy, and neonatal conditions, such as prematurity and low birth weights, affect mortality and morbidity of patients with CHD (4, 6-8).

However, a disparity exists in the survival and prognosis of CHD patients depending on the country and medical system (1, 9). Studies on the survival of patients with CHD are mostly concentrated on data from well-developed countries in the West, and there are few reports from non-Western countries, including Korea. The Republic of Korea has a well-developed health insurance system where almost all citizens benefit from the national health insurance, and the survival rate of patients with CHD has improved rapidly

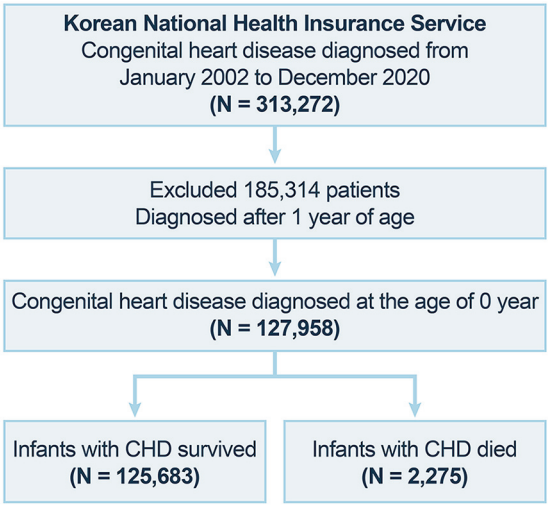

Figure 1. *Study flow chart.*

Table I. *ICD-10 codes of the included variables.*

Hierarchical classification		
Lesion 1 (Conotruncal)	Common arterial trunk	Q20.0
	Aortopulmonary septum defect	Q21.4
	Double outlet right ventricle	Q20.1
	Double outlet left ventricle	Q20.2
	Transposition of great arteries	Q20.3
	Congenitally corrected transposition	Q20.5
	Tetralogy of fallot	Q21.3
Lesion 2 (Severe non-conotruncal)	Endocardial cushion defect	Q21.2
	Single ventricle	Q20.4
	Hypoplastic left heart syndrome	Q23.4
Lesion 3	Coarctation of the aorta	Q25.1
Lesion 4	Ventricular septal defect	Q21.0
Lesion 5	Atrial septal defect	Q21.1
Lesion 6	All other congenital heart disease diagnoses that are not included in the above five lesion groups	

over recent decades (1, 10). In a study of patients with CHD of all ages, the mortality rate was 451.0 per 100,000 person-years in Korea (10). However, no Asian study has reported whether the prognosis for infants born with CHD to survive into adulthood differs depending on CHD severity or neonatal conditions other than CHD.

Therefore, this study aimed to analyze the survival of infants with CHD until the age of 18 years using large-scale population data in Korea and investigate the effect of neonatal conditions at birth.

Patients and Methods

Study population. This study was conducted retrospectively by extracting the Korean National Health Insurance Service (NHIS) claims data from January 2002 to December 2020. The Korean NHIS serves almost all the citizens of the Republic of Korea, with approximately 50 million registered citizens. The Korean NHIS includes diagnostic codes according to the International Classification of Disease, Tenth Revision (ICD-10); demographic characteristics; and information on prescriptions, tests, and surgeries performed during outpatient visits or hospitalizations. Among all individuals diagnosed with CHD based on the ICD-10 codes, we included only those diagnosed with CHD at less than one year of age. The follow-up duration was from the date they were first diagnosed with CHD to the date they died or were censored before the age of 18 years. The flowchart of this study is presented in Figure 1. This study was approved by the Institutional Review Board of Korea University Anam Hospital (approval no. 2021AN0418). The requirement for informed consent was waived because of the retrospective study design.

Definition. CHD classification. CHD was diagnosed by assigning the corresponding ICD-10 codes (Table I). We classified infants diagnosed with CHD at less than 1 year of age according to the modified hierarchical classification that had been used in previous studies (2, 3, 5, 11). Lesion 1, a conotruncal lesion, included the common arterial trunk, aortopulmonary septum defect, double outlet right ventricle, double outlet left ventricle, transposition of the great arteries, congenitally corrected transposition, and tetralogy of Fallot. Lesion 2, a severe non-conotruncal lesion, included an endocardial cushion defect, a single ventricle, and hypoplastic left heart syndrome. Lesion 3 refers to the coarctation of the aorta, Lesion 4 a ventricular septal defect, lesion 5 an atrial septal defect, and Lesion 6 included all other congenital heart anomalies not included in lesions 1-5. We considered Lesions 1 and 2 as complex lesions.

Neonatal risk factors. We used twins, preterm birth (<28 weeks, 28-37 weeks), birth asphyxia, small for gestation age (SGA), large for gestational age (LGA), low birth weight (<2,500 g), respiratory distress, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), bacterial sepsis, intracranial hemorrhage, disseminated intravascular coagulation, necrotizing enterocolitis, seizure, and pulmonary hypertension as variables based on the ICD-10 code for neonatal condition. Moreover, we also analyzed differences based on birth year divided as 2002-2005, 2006-2010, 2011-2015, and 2016-2020.

Statistical analysis. The continuous variables are summarized as means±standard deviations or as medians and interquartile ranges, while the categorical variables are presented as frequencies and proportions. For continuous variables, either the Student's *t*-test or Mann-Whitney *U*-test was applied, and for categorical variables, either the chi-squared test or Fisher's exact test was used. Survival rates were calculated using the Kaplan-Meier method and the Cox proportional hazards regression model was used for univariate and multivariate analyses. Variables with *p*-values of less than 0.10 in univariate analysis were included in the multivariate analysis. All analyses were performed using R statistical software (www.R-project.org).

Results

Between 2002 and 2020, 127,958 infants were diagnosed with CHD. Among them, 2,275 died before the age of 18

Table II. *Baseline characteristics*.

	Survival (n=125,683)	Death (n=2,275)	*p*-Value
Sex			0.020
Male	61,615 (49.0)	1,172 (51.5)	
Female	64,068 (51.0)	1,103 (48.5)	
CHD lesion			<0.001
Complex (Lesions 1-2)	6,625 (5.3)	987 (43.4)	
Lesion 1	4,921 (3.9)	568 (25.0)	
Lesion 2	1,704 (1.4)	419 (18.4)	
Non-complex (Lesions 3-6)	119,058 (94.7)	1,288 (56.6)	
Lesion 3	1,452 (1.2)	115 (5.1)	
Lesion 4	32,862 (26.1)	325 (14.3)	
Lesion 5	63,692 (50.7)	325 (14.3)	
Lesion 6	21,053 (16.8)	618 (27.2)	
Cardiac surgery			<0.001
Yes	30,331 (24.1)	2,049 (90.1)	
No	95,352 (75.9)	226 (9.9)	
Twin			0.039
Yes	1,913 (1.5)	22 (1.0)	
No	123,770 (98.5)	2,253 (99.0)	
Preterm (<28 wk)			0.503
Yes	570 (0.5)	13 (0.6)	
No	125,113 (99.5)	2,262 (99.4)	
Preterm (28-37 wk)			<0.001
Yes	11,204 (8.9)	108 (4.7)	
No	114,479 (91.1)	2,167 (95.3)	
Birth asphyxia			0.063
Yes	407 (0.3)	13 (0.6)	
No	114,479 (91.1)	2,167 (95.3)	
Small for gestational age			0.152
Yes	658 (0.5)	18 (0.8)	
No	124,998 (99.5)	2,257 (99.2)	
Large for gestational age			0.235
Yes	289 (0.2)	2 (0.1)	
No	125,394 (99.8)	2,273 (99.9)	
Low birth weight (<2,500 g)			0.037
Yes	5,160 (4.1)	73 (3.2)	
No	120,523 (95.9)	2,202 (96.8)	
Respiratory distress			0.003
Yes	11,326 (9.0)	164 (7.2)	
No	114.357 (91.0)	2,111 (92.8)	
Pulmonary hemorrhage			<0.001
Yes	17 (0.0)	3 (0.1)	
No	125,666 (100.0)	2,272 (99.9)	
Bronchopulmonary dysplasia			0.002
Yes	578 (0.5)	21 (0.9)	
No	125,105 (99.5)	2,254 (99.1)	
Bacterial sepsis			0.974
Yes	2,060 (1.6)	38 (1.7)	
No	123,623 (98.4)	2,237 (98.3)	
Intracranial nontraumatic hemorrhage			0.608
Yes	379 (0.3)	5 (0.2)	
No	125,304 (99.7)	2,270 (98.3)	
Disseminated intravascular coagulation			1.000
Yes	22 (0.0)	0 (0.0)	
No	125,661 (100.0)	2,275 (100.0)	
Necrotizing enterocolitis			0.320
Yes	113 (0.1)	4 (0.2)	
No	125,570 (99.9)	2,271 (99.8)	
Convulsions			0.110
Yes	353 (0.3)	11 (0.5)	
No	125,330 (99.7)	2,264 (99.5)	
Pulmonary hypertension			<0.001
Yes	318 (0.3)	40 (1.8)	
No	125,365 (99.7)	2,235 (98.2)	
Diagnosis year			<0.001
2002-2005	8,603 (6.8)	396 (17.4)	
2006-2010	24,367 (19.4)	741 (32.6)	
2011-2015	39,775 (31.6)	704 (30.9)	
2016-2020	52,938 (42.1)	434 (19.1)	

CHD: Congenital heart disease.

years (Table II). In brief, 568 (25.0%) deaths occurred in the Lesion 1 group, which was the highest number of deaths, followed by 419 (18.4%) in the Lesion 2 group, which was the second highest number of deaths. The next highest number of deaths occurred in the Lesion 6, 4-5, and 3 groups, in that order. The proportion of infants who had undergone cardiac surgery was significantly higher in the mortality group than in the survival group (90.1% *vs*. 24.1%, $p<0.001$). Among the neonatal conditions, twins, preterm birth (28-37 weeks), low birth weight, respiratory distress, pulmonary hemorrhage, BPD, and pulmonary hypertension showed significant differences between the survival and mortality groups. Moreover, based on the year of diagnosis, the order of the highest number of deaths was 2006-2010, 2011-2015, 2015-2020, and 2002-2005.

Characteristics according to CHD lesions. The differences according to CHD lesions are presented in Table III. Lesion 5 was present in the highest number of patients, followed by Lesions 4, 1, 6, 2, and 3. The highest proportion of patients who had undergone cardiac surgery was in Lesion 1, followed by Lesion 3 and 2 groups. The highest proportion of deaths was observed in the Lesion 2 group (19.7%), followed by Lesion 1 (10.3%), 3 (7.3%), 6 (2.9%), 4 (1.0%), and 6 (0.4%) groups.

Table III. *Clinical characteristics according to the complexity of congenital heart disease.*

Lesion	1 (N=5,489)	2 (N=2,123)	3 (N=1,567)	4 (N=33,186)	5 (N=63,922)	6 (N=21,671)	*p*-Value
Sex							<0.001
Male	3,233 (58.9)	1,046 (49.3)	899 (57.4)	15,507 (46.7)	31,540 (49.3)	10,562 (48.7)	
Female	2,256 (41.1)	1,077 (50.7)	668 (42.6)	17,679 (53.3)	32,382 (50.7)	11,109 (51.3)	
Cardiac surgery							<0.001
Yes	5,115 (93.2)	1,692 (79.7)	1,282 (81.8)	9,814 (29.6)	7,768 (12.2)	6,709 (31.0)	
No	374 (6.8)	431 (20.3)	285 (18.2)	23372 (70.4)	56154 (87.8)	14962 (69.0)	
Twin							<0.001
Yes	37 (0.7)	13 (0.6)	17 (1.1)	407 (1.2)	1,163 (1.8)	298 (1.4)	
No	5,452 (99.3)	2,110 (99.4)	1,550 (98.9)	32,779 (98.8)	62,759 (98.2)	21,373 (98.6)	
Preterm (<28 wk)							<0.001
Yes	5 (0.1)	1 (0.0)	0 (0.0)	22 (0.1)	302 (0.5)	253 (1.2)	
No	5,484 (99.9)	2,122 (100.0)	1,567 (100.0)	33,164 (99.9)	63,620 (99.5)	21,418 (98.8)	
Preterm (28-37 wk)							<0.001
Yes	168 (3.1)	76 (3.6)	80 (5.1)	1,176 (3.5)	7,745 (12.1)	2,067 (9.5)	
No	5,321 (96.9)	2,047 (96.4)	1,487 (94.9)	32,010 (96.5)	56,177 (87.9)	19,604 (90.5)	
Birth asphyxia							<0.001
Yes	8 (0.1)	6 (0.3)	3 (0.2)	41 (0.1)	281 (0.4)	81 (0.4)	
No	5,481 (99.9)	2,117 (99.7)	1,564 (99.8)	33,145 (99.9)	63,641 (99.6)	21,590 (99.6)	
Small for gestational age							<0.001
Yes	13 (0.2)	11 (0.5)	15 (1.0)	103 (0.3)	484 (0.8)	77 (0.4)	
No	5,476 (99.8)	2,112 (99.5)	1,552 (99.0)	33,083 (99.7)	63,438 (99.2)	21,594 (99.6)	
Large for gestational age							<0.001
Yes	3 (0.1)	4 (0.2)	0 (0.0)	32 (0.1)	182 (0.3)	70 (0.3)	
No	5,486 (99.9)	2,119 (99.8)	1,567 (100.0)	33,154 (99.9)	63,740 (99.7)	21,601 (99.7)	
Low birth weight (<2,500 g)							<0.001
Yes	112 (2.0)	31 (1.5)	57 (3.6)	616 (1.9)	3,302 (5.2)	1,115 (5.1)	
No	5,377 (98.0)	2,092 (98.5)	1,510 (96.4)	32,570 (98.1)	60,620 (94.8)	20,556 (94.9)	
Respiratory distress							<0.001
Yes	144 (2.6)	68 (3.2)	85 (5.4)	1,189 (3.6)	7,399 (11.6)	2,605 (12.0)	
No	53,45 (97.4)	2,055 (96.8)	1,482 (94.6)	31,997 (96.4)	56,523 (88.4)	19,066 (88.0)	
Pulmonary hemorrhage							0.074
Yes	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (0.0)	7 (0.0)	
No	5,488 (100.0)	2,123 (100.0)	1,567 (100.0)	33,186 (100.0)	63,910 (100.0)	21,664 (100.0)	
Bronchopulmonary dysplasia							<0.001
Yes	11 (0.2)	2 (0.1)	6 (0.4)	37 (0.1)	297 (0.5)	246 (1.1)	
No	5,478 (99.8)	2,121 (99.9)	1,561 (99.6)	33,149 (99.9)	63,625 (99.5)	21,425 (98.9)	
Bacterial sepsis							<0.001
Yes	57 (1.0)	45 (2.1)	28 (1.8)	446 (1.3)	1,233 (1.9)	289 (1.3)	
No	5,432 (99.0)	2,078 (97.9)	1,539 (98.2)	32,740 (98.7)	62,689 (98.1)	21,382 (98.7)	

Table III. *Continued*

Survival and risk factors for mortality during childhood for infants with CHD. The survival rate during childhood for infants with CHD was 97.9% (Figure 2). There was a sharp decline in the survival rates during the first year of life, followed by a gradual decline thereafter. The survival rates according to each characteristic of patients with CHD are presented in Figure 3, and the hazard ratios (HRs) for various factors related to childhood mortality in infants with CHD are shown in Table IV. Univariable analysis revealed that male sex, birth asphyxia, pulmonary hemorrhage, BPD, pulmonary hypertension, and complex CHD (Lesions 1-2) increased the likelihood of mortality. However, twin pregnancy, preterm birth (28-37 weeks), and respiratory distress decreased the likelihood of mortality in infants with congenital heart disease. Additionally, the risk of mortality decreased with more recent diagnoses. Multivariable analysis revealed that complex CHD was the most powerful risk factor for childhood mortality, followed by pulmonary hypertension. Other risk factors for mortality in infants with CHD were birth asphyxia, SGA, respiratory distress, pulmonary hemorrhage, BPD, and convulsions. Preterm birth (28-37 weeks) was significantly associated with a decreased risk of mortality in multivariate analysis. Moreover, the risk of mortality decreased significantly with more recent diagnoses, even in multivariate analysis.

Table III. *Continued*

Lesion	1 (N=5,489)	2 (N=2,123)	3 (N=1,567)	4 (N=33,186)	5 (N=63,922)	6 (N=21,671)	*p*-Value
Intracranial nontraumatic hemorrhage							<0.001
Yes	5 (0.1)	0 (0.0)	3 (0.2)	25 (0.1)	275 (0.4)	76 (0.4)	
No	5,484 (99.9)	2,123 (100.0)	1,564 (99.8)	33,161 (99.9)	63,647 (99.6)	21,595 (99.6)	
Disseminated intravascular coagulation							0.655
Yes	1 (0.0)	0 (0.0)	1 (0.1)	4 (0.0)	11 (0.0)	5 (0.0)	
No	5,488 (100.0)	2,123 (100.0)	1,566 (99.9)	33,182 (100.0)	63,911 (100.0)	21,666 (100.0)	
Necrotizing enterocolitis							0.008
Yes	8 (0.1)	3 (0.1)	1 (0.1)	14 (0.0)	62 (0.1)	29 (0.1)	
No	5,481 (99.9)	2,120 (99.9)	1,566 (99.9)	33,172 (100.0)	63,860 (99.9)	21,642 (99.9)	
Convulsions							<0.001
Yes	5 (0.1)	3 (0.1)	5 (0.3)	53 (0.2)	230 (0.4)	68 (0.3)	
No	5,484 (99.9)	2,120 (99.9)	1,562 (99.7)	33,133 (99.8)	63,692 (99.6)	21,603 (99.7)	
Pulmonary hypertension							<0.001
Yes	15 (0.3)	18 (0.8)	16 (1.0)	130 (0.4)	95 (0.1)	84 (0.4)	
No	5,474 (99.7)	2,105 (99.2)	1,551 (99.0)	33,056 (99.6)	63,827 (99.9)	21,587 (99.6)	
Death							<0.001
Yes	568 (10.3)	419 (19.7)	115 (7.3)	325 (1.0)	230 (0.4)	618 (2.9)	
No	4,921 (89.7)	1,704 (80.3)	1,452 (92.7)	32,861 (99.0)	63,692 (99.6)	21,053 (97.1)	
Diagnosis year							<0.001
2002-2005	804 (14.6)	350 (16.5)	157 (10.0)	4,057 (12.2)	2,217 (3.5)	1,414 (6.5)	
2006-2010	1,492 (27.2)	750 (35.3)	398 (25.4)	8,665 (26.1)	9,180 (14.4)	4,623 (21.3)	
2011-2015	1,672 (30.5)	636 (30.0)	532 (34.0)	10,511 (31.7)	20,113 (31.5)	7,015 (32.4)	
2016-2020	1,521 (27.7)	387 (18.2)	480 (30.6)	9,953 (30.0)	32,412 (50.7)	8,619 (39.8)	

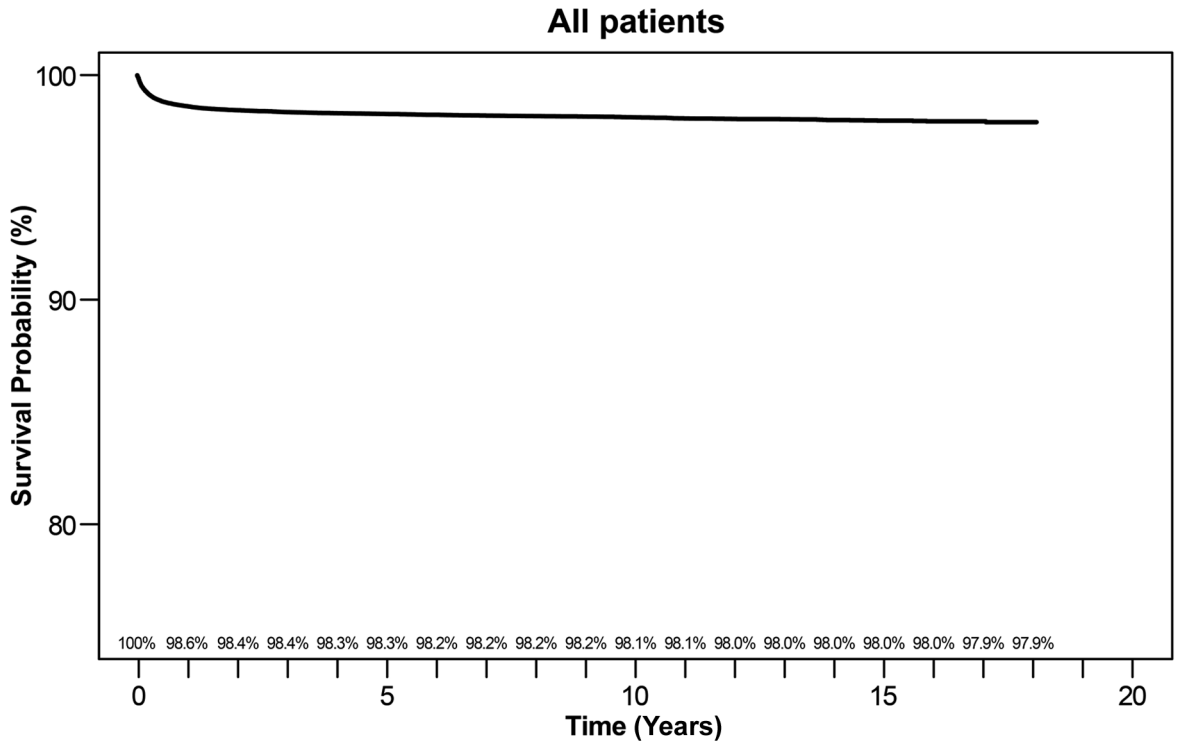

Figure 2. *Survival rates of infants with congenital heart disease (CHD) during childhood.*

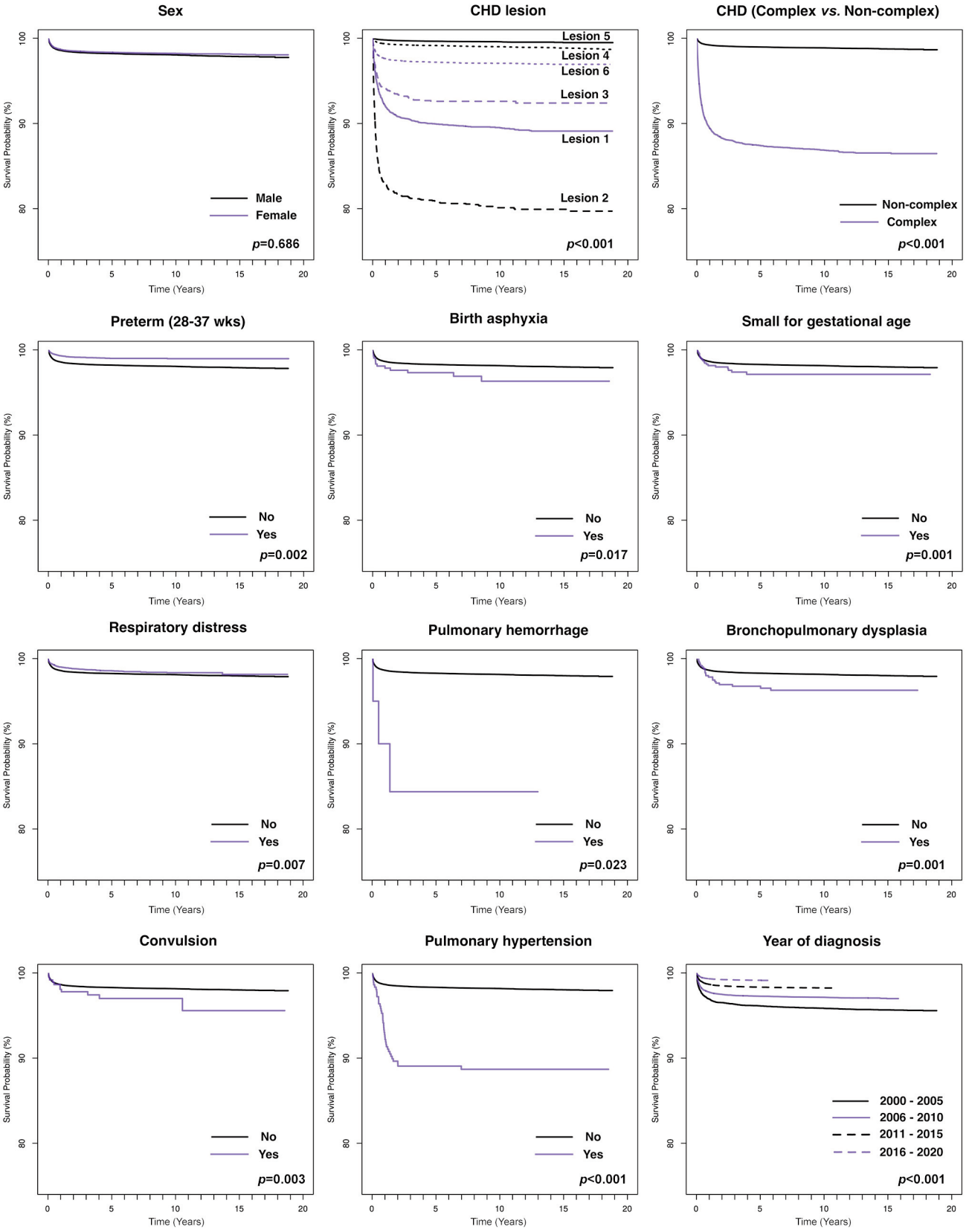

Figure 3. *Cumulative incidence of childhood mortality according to neonatal conditions.*

Table IV. *Univariate and multivariate analyses for mortality.*

	Univariate			Multivariate		
Variable	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Female	0.905	(0.833-0.982)	0.017	1.017	(0.936-1.104)	0.686
Twin	0.656	(0.431-0.998)	0.049	1.019	(0.669-1.553)	0.928
Preterm (<28 wk)	1.285	(0.745-2.216)	0.367			
Preterm (28-37 wk)	0.524	(0.432-0.636)	<0.001	0.732	(0.601-0.893)	0.002
Birth asphyxia	1.753	(1.016-3.025)	0.043	1.944	(1.123-3.365)	0.017
Small for gestational age	1.507	(0.947-2.397)	0.083	2.137	(1.342-3.404)	0.001
Large for gestational age	0.390	(0.097-1.563)	0.184			
Low birth weight (<2,500 g)	0.798	(0.632-1.007)	0.058	1.111	(0.874-1.411)	0.388
Respiratory distress	0.814	(0.695-0.955)	0.012	1.256	(1.063-1.484)	0.007
Pulmonary hemorrhage	9.285	(2.992-28.813)	<0.001	3.839	(1.204-12.245)	0.023
Bronchopulmonary dysplasia	1.972	(1.283-3.030)	0.002	2.175	(1.390-3.403)	0.001
Bacterial sepsis	0.998	(0.724-1.375)	0.991			
Intracranial nontraumatic hemorrhage	0.754	(0.313-1.815)	0.530			
Disseminated intravascular coagulation	1.67×10^{-5}		0.977			
Necrotizing enterocolitis	1.928	(0.723-5.142)	0.189			
Convulsions	1.740	(0.962-3.147)	0.067	2.470	(1.362-4.481)	0.003
Pulmonary hypertension	6.297	(4.606-8.609)	<0.001	4.184	(3.034-5.769)	<0.001
Complex CHD	12.448	(11.457-13.526)	<0.001	10.736	(9.849-11.703)	<0.001
Diagnosis year						
2002-2005	Ref.					
2006-2010	0.683	(0.605-0.773)		0.805	(0.711-0.910)	0.001
2011-2015	0.418	(0.369-0.474)		0.589	(0.519-0.669)	<0.001
2016-2020	0.215	(0.187-0.247)		0.348	(0.302-0.401)	<0.001

HR: Hazard ratio; CI: confidence interval; CHD: congenital heart disease.

Discussion

In this study, using Korean NHIS claims data, out of 127,958 infants diagnosed with CHD, 2,275 died before 18 years of age. The survival rate for infants with CHD in South Korea was 97.9%. The survival rate declined sharply during the first year of life, followed by a gradual and stable decline thereafter. The highest childhood mortality rate was observed in Lesion 2 group (non-conotruncal defect) at 19.7%, followed by Lesion 1 group (conotruncal defect) at 10.2%. The mortality rates for Lesion 3 (coarctation of the aorta), 6 (all other lesions), 4 (ventricular septal defect), and 5 (atrial septal defect) groups were 7.3%, 2.9%, 1.0%, and 0.4%, respectively. According to multivariable analysis, the significant risk factors for childhood mortality in infants with CHD were complex CHD, pulmonary hypertension, birth asphyxia, SGA, respiratory distress, pulmonary hemorrhage, BPD, and convulsions. Additionally, the mortality rate during childhood significantly decreased in more recent birth years.

The survival rate for children with CHD has significantly improved compared to the past, particularly in those less than one year old (4, 5). Consequently, the mortality rate of relatively older children (>5 years old) is reportedly higher than that in the past (4). However, the mortality rate, especially in children aged four or younger, remains the highest. In our study, the highest mortality rate was observed during the first year of life, and the mortality rates for each variable showed a sharp decline before the age of 5 years. The mortality rate of young children with CHD under 5 years of age is still steep, emphasizing the importance of early intervention and management for infants born with CHD to improve their future survival rates.

Although the survival rate of CHD patients has improved dramatically, the mortality rate in patients with CHD remains significantly higher than that of the general population. The mortality risk is reported to be 17.7 times higher (95%CI=16.8-18.6) than that of the general population, indicating a significant difference in survival rates between children with CHD and the general population (2, 4). According to a study in Sweden, the mortality rate of children with non-conotruncal CHD lesions was associated with the highest hazard ratio (HR=97.2, 95%CI=80.4-117.4) compared to that of the general population. Conversely, another study in Sweden focused on adults with CHD found that those with conotruncal defects had the highest mortality rate (HR=10.13, 95%CI=8.78-11.69) compared to that of the general population (2, 3). Another study in the United States reported that the mortality for single-ventricle physiology among CHDs was the highest across all age groups of children. Specifically, the mortality rates in infants with single-ventricle defects had

significantly decreased, but those in older children and adolescents had actually increased compared to those in previous years (4). The authors suggested several potential reasons for the observed increase, including the early timing of Fontan surgery, development of failing Fontan physiology, and difficulties in accessing healthcare due to insurance issues. The risk factors for mortality in children with CHD purportedly include low birth weight, male sex, prematurity, extracardiac defects, and genetic anomalies (4, 7).

To our knowledge, this study is the first large-scale investigation of survival and neonatal risk factors in infants with CHD in an Asian country with a developed health insurance system. In this study, as in previous Western studies, the highest infant mortality rate was associated with non-conotruncal defects, and complex CHD, including Lesions 1 (conotruncal) and 2 (non-conotruncal), was the most important risk factor for mortality in infants with CHD during childhood (HR=10.736, 95%CI=9.849-11.703). The second most significant risk factor was pulmonary hypertension. The annual incidence of pulmonary arterial hypertension associated with CHD in children is reportedly 2.2 per million, which is higher than the prevalence in adult patients with CHD (12). Pulmonary hypertension in pediatric patients with CHD is further complicated by the complexity of CHD, prematurity, underlying lung diseases, such as BPD, chromosomal anomalies, and other comorbidities, making treatment more challenging (13). Sildenafil and bosentan are reportedly helpful in improving symptoms of pulmonary hypertension in Fontan patients (14, 15). While small-scale reports have suggested the effectiveness of riociguat and selexipag for pediatric pulmonary arterial hypertension, data on pediatric patients with CHD is lacking (16-20). Future assessment of the efficacy and clinical use of these pulmonary hypertension medications in pediatric patients with CHD, as well as individualized evaluation and appropriate treatment strategies in patients with CHD, may contribute to improving the survival rates in pediatric patients with CHD. Moreover, the mortality rate was higher in cases with other underlying conditions during the neonatal period, such as birth asphyxia, SGA, respiratory distress, pulmonary hemorrhage, BPD, and convulsions. Therefore, individualized and optimal evaluation and treatment strategies may be necessary for children with CHD and other comorbidities in the future.

Contrary to our initial expectations, premature infants born between 28-37 weeks had a lower likelihood of mortality. While causal relationships could not be confirmed in this observational study, premature infants may have a higher incidence of mild CHD incidentally detected during routine echocardiography screenings performed during admission to the neonatal intensive care unit, who may not require treatment. We attempted to adjust for CHD severity by classifying Lesions 1-2 as complex CHD using multivariable analysis. However, even within non-complex Lesions 2-6, the severity of heart anomalies in full-term infants was higher than that in premature infants with coincidentally detected heart anomalies, suggesting that the impact of the anomaly on survival was more significant in full-term infants than in premature infants.

We investigated neonatal risk factors for childhood mortality in infants with CHD. Complex CHD and pulmonary hypertension were the most significant risk factors of mortality in infants with CHD, and the presence of other neonatal morbidities also contributed to a significantly higher risk of childhood mortality. This study suggests the possibility of a more detailed and precise risk stratification for infants with CHD based on certain characteristics in the neonatal period, which may lead to higher childhood mortality. Through sophisticated and individualized risk assessments for these neonatal risk factors and the development of optimal treatment strategies, we may improve the survival of infants born with CHD in the future.

Study limitations. First, this was a retrospective observational study, which entails a potential for information bias. Second, it was based on the Korean NHIS, which has the advantage of being a large-scale dataset covering almost all Korean citizens but may lack detailed information on some factors. Additionally, the NHIS data do not provide information on patients' lifestyle habits, such as dietary patterns and physical activity. Third, the mortality of infants with CHD may be influenced not only by infantile diseases, but also by new diseases during childhood. However, in this study, we did not consider concurrent diseases after infancy. Several childhood diseases not included in this study might have affected the mortality rate of infants with CHD. Finally, we classified CHD hierarchically; however, CHD is a heterogeneous disease, and the disease severity can vary greatly, even within each lesion. However, this aspect could not be assessed using the NHIS data.

Conclusion

The survival of infants with CHD has been favorable in South Korea, with a survival rate of over 97% over the past 20 years. Complex CHD and pulmonary hypertension are the most significant risk factors for mortality in infants with CHD, and several other neonatal conditions are also significant risk factors. Individualized risk assessment that considers these factors and optimal treatment strategies may contribute to improving the survival rates of children with CHD.

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Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, J.S.L., O.K.N and J.E.P.; Methodology, O.K.N.; Software, J.S.L. and O.K.N.; Validation, H.C, J.S.H., K.S.H. and G.Y.J.; Formal Analysis, O.K.N.; Investigation, J.S.L., J.K. and O.K.N.; Resources, J.E.P.; Data Curation, J.S.L. and O.K.N.; Writing – Original Draft Preparation, J.S.L. and O.K.N.; Writing – Review & Editing, J.E.P.; Visualization, J.S.L., O.K.N and J.E.P.; Supervision, O.K.N and J.E.P.; Project Administration, J.S.L., O.K.N and J.E.P.; Funding Acquisition, J.E.P.

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