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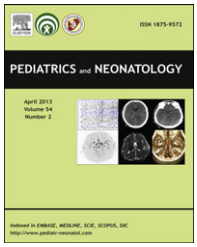

ORIGINAL ARTICLE

Prevalence, Mortality, and the Disease Burden of Pediatric Congenital Heart Disease in Taiwan

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Key Words
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Background: In Taiwan, the incidence of congenital heart diseases (CHDs) and severe CHDs was 13.08 and 1.51 per 1000 live births, respectively. This study further elucidates the prevalence and mortality of pediatric CHD patients in Taiwan.
Methods: From the National Health Insurance database 2000—2010, we retrieved the data of CHD patients (aged 0—18 years). Mortality data were obtained from the national death statistics.
Results: In total, 45,119 pediatric CHD patients were identified, given the prevalence at 918.0 per 100,000 (107.1 for severe CHD and 853.8 for simple CHD). Ventricular septal defect, ostium secundum-type atrial septal defect, patent ductus arteriosus, pulmonary stenosis, and tetralogy of Fallot were the five most frequently diagnosed CHDs. In those aged 0—6 years, the prevalence was 1233.7 per 100,000 (123.5 for severe CHD and 1149.6 for simple CHD). The age-specific prevalence of both simple and severe CHDs declined rapidly after the age of 10 years. From the death registry, we noted that more than 90% of CHD-related deaths occurred before the age of 5 years. The probability of cardiac death in CHD patients during

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infancy was 4.5%, with the cumulative probability reaching 5.44%, 5.68%, and 6.04% by the ages of 5, 10, and 20 years, respectively.
Conclusion: Because most CHD deaths occurred within the first 5 years of life (mainly during infancy), the relatively low prevalence of CHDs in the population aged 0—18 years (918/100,000; 74% for those between 0 years and 6 years of age) and the rapid decline in the age-specific prevalence of CHD after the age of 10 years was attributed to noncompliance of the children to medical follow-up after they began schooling.

1. Introduction

Congenital heart disease (CHD) is a major concern in pediatric health care and has a significant impact on infant morbidity and mortality worldwide.[1—3] Recent advances in fetal diagnosis and postnatal cardiac intervention may modify the CHD spectrum and subsequent medical needs.[4—7] The incidence of CHD varies between geographic regions, and this variation has been attributed to the number of patients with ventricular septal defects (VSD).[8] The reported incidence of CHD among infants ranges from four to 12 per 1000 live births and is estimated to be approximately 10 per 1000 live births.[5,9] A national population study conducted from 2000 to 2006 in Taiwan showed that the incidence of CHD was 13.08 per 1000 live births, with incidences of severe CHDs and simple CHDs at 1.51 and 11.67 per 1000 live births, respectively.[10] The reported prevalence of CHD varies because of differences in the length of follow-up periods, as well as methods of target population selection and case detection.[2,5,11] Several multistage surveys have been conducted in school-aged children in Taiwan[12,13]; the prevalence of CHD ranged from 2.4 to 6.04 per 1000 children.[12,13] The discrepancy between the incidence and prevalence data may be attributed to disease-related deaths and case identification criteria, as set by the study methods. A population-based study using a registry database may avoid referral and diagnostic bias caused by geographic regional variations and small sample sizes. The National Health Insurance (NHI) is managed by the Bureau of National Health Insurance, Department of Health. Since 1995, more than 98% of Taiwanese nationals have been obligated by law to join the government-run, single-payer NHI program.[14] The Taiwan National Department of Health established a national mortality database, which includes data on age-specific mortality and causes of death. These national databases serve as ideal resources for nationwide epidemiological studies. Using these databases, we investigated the overall and age-specific prevalence of CHD and CHD subtypes. The probability of death from CHD was estimated in order to elucidate its impact on disease prevalence.

2. Methods

2.1. NHI database

Health care records for the period between January 1, 2000 and December 31, 2010, were retrieved for analysis. We limited our record retrieval to the birth cohort between 1992 and 2010. The completely computerized NHI database consists of health records from each medical visit, a scrambled identification number, and information including the patient's date of birth, gender, date of admission or outpatient department visits, and reimbursement. Patients diagnosed with any type of CHD (according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code) were selected. To avoid errors caused by incorrect tentative diagnoses, insignificant asymptomatic CHD, and miscoding, we defined prevalent CHD patients as those hospitalized with CHD as the major disease or those who visited the outpatient department with a major diagnosis of CHD consistently at least three times within the study period. The CHD was further classified as "simple" or "severe" based on the diagnostic code (Table 1).[10]

2.2. Age-specific prevalence

The gender-specific population sizes by a single year of age were obtained from the Statistical Yearbook of Interior, Department of Statistics, Ministry of the Interior.[15] In 2010, a total of 4,915,037 children between 0 years and 18 years made up the denominator used for calculating prevalence and age-specific prevalence.

2.3. Death statistics

The number of deaths from CHD (ICD 10, Q20—Q28) and all causes were available from the Death Statistics for 2008 and 2009 compiled by the Department of Health.[16] For calculating age-specific CHD mortality, the population size obtained in 2008 and 2009 were used as the denominator. We constructed a hypothetic birth cohort of 100,000 newborns with CHD incidence at 1308 per 100,000[10] and calculated the age-specific mortality for CHD and for all other causes from the death statistics data 2008—2009. We estimated the number of CHD deaths, the number of deaths from other causes, and the number of patients alive after considering the competing risks in each age strata. We divided the number of CHD deaths by the number of patients at risk of each age strata to obtain age-specific estimates of death probability from CHD. The cumulative death probability from CHD was defined as the cumulative number of CHD deaths divided by 1308.

Table 1 CHD disease-specific prevalence rate (per 100,000) and test for gender predominance.

ICD-9-CM code	Disease	Severe (S)/ Simple (E)	Prevalence (10^{-5})			p	Prevalence (10^{-5}) for children of 0–6 years old (95% CI)	
			Total	Male	Female			
745	Bulbus cordis anomalies and anomalies of cardiac septal closure (excluding 745.0, 745.1, 745.2, 745.3, 745.4, 745.5, 745.6)	E	24.0	22.5	25.6	0.0265	21.3	(19.1–23.9)
745.0	Common truncus	S	7.3	7.0	7.7	0.6500	6.0	(4.8–7.4)
745.1	Transposition of great arteries (including 745.10, but excluding 745.11, 745.12)	S	15.5	19.8	10.9	<0.0001	18.7	(16.5–21.1)
745.11	Double outlet right ventricle	S	9.5	10.1	8.9	0.1517	13.7	(11.9–15.8)
745.12	Corrected transposition of great arteries	S	1.9	2.2	1.5	0.0741	2.5	(1.8–3.5)
745.2	Tetralogy of Fallot	S	51.4	55.9	46.5	<0.0001	54.9	(51.1–58.9)
745.3	Common ventricle	S	6.5	7.0	6.0	0.1573	6.5	(5.3–8.0)
745.4	Ventricular septal defect	E	329.9	316.2	344.8	<0.0001	426.1	(415.4–437.1)
745.5	Ostium secundum-type atrial septal defect	E	318.0	277.9	361.5	<0.0001	477.8	(466.5–489.4)
745.6	Endocardial cushion defect	S	15.6	13.1	18.3	<0.0001	16.0	(14.1–18.3)
746.0	Pulmonary stenosis	E	79.3	76.0	82.8	0.0075	94.4	(89.5–99.7)
746.1	Tricuspid atresia or stenosis	S	3.5	4.1	2.9	0.0363	4.2	(3.2–5.4)
746.2	Congenital Ebstein's anomaly	E	3.7	3.1	4.4	0.0234	3.2	(2.4–4.3)
746.3	Aortic stenosis	E	10.1	12.4	7.6	<0.0001	8.2	(6.8–9.8)
746.4	Congenital insufficiency of aortic valve	E	3.0	3.5	2.5	0.0442	1.2	(0.8–2.0)
746.5	Congenital mitral stenosis	S	1.4	1.3	1.5	0.6355	1.6	(1.0–2.4)
746.6	Congenital mitral insufficiency	E	10.9	8.4	13.7	<0.0001	6.1	(4.9–7.6)
746.7	Hypoplastic left heart syndrome	S	3.1	3.0	3.2	0.6586	5.1	(4.0–6.4)
746.81	Subaortic stenosis	E	1.2	1.2	1.2	0.9509	1.4	(0.9–2.1)
746.82	Cor triatriatum	E	1.2	1.1	1.4	0.3980	1.2	(0.8–2.0)
746.83	Infundibular pulmonic stenosis	E	4.4	4.4	4.3	0.9513	5.3	(4.2–6.7)
747.0	Patent ductus arteriosus	E	129.5	97.1	164.7	<0.0001	153.4	(147.0–160.0)
747.1	Coarctation of aorta	E	21.4	22.4	20.3	0.1140	32.3	(29.5–35.5)
747.3	Anomalies of pulmonary artery	E	45.5	44.4	46.7	0.2429	51.2	(47.6–55.1)
747.41	Total anomalous pulmonary venous connection	S	7.4	7.8	7.1	0.3603	11.5	(9.8–13.4)
747.42	Partial anomalous pulmonary venous connection	E	2.4	2.0	2.7	0.1168	2.9	(2.2–4.0)
	Subtotal of severe CHD		107.1	114.0	99.7	<0.0001	123.5	(117.8–129.5)
	Subtotal of simple CHD		853.8	770.3	944.8	<0.0001	1149.6	(1132.0–1167.4)
	Total		918.0	839.7	1003.2	<0.0001	1233.7	(1215.5–1252.1)

A p value <0.002 was defined as significant with Bonferroni correction for multiple comparisons.
CHD = congenital heart disease.

2.4. Statistical analyses

We used the SAS software (SAS, Cary, NC, USA) for statistical analyses. The overall and age-specific prevalence of each CHD subtype were calculated. The age-specific and gender-specific prevalence rates were estimated based on the age of prevalent patients in 2010. We estimated prevalence and its 95% confidence intervals (CI) for each diagnostic code using PROC GENMOD with binomial distribution. All tests were two-sided. A statistically significant p value of <0.002 was defined, after including Bonferroni correction for multiple comparisons.

Age-specific mortality and overall mortality due to CHD were calculated. The CHD mortality fraction was obtained by dividing the number of patients who died from CHD by the total number of deaths.

3. Results

A total of 45,119 prevalent patients who fulfilled the inclusion criteria were identified.

3.1. Prevalence of CHD in pediatric populations

The overall prevalence of pediatric CHD per 100,000 children was 918.0 (95% CI, 909.6—926.4), and the prevalence of simple CHD and severe CHD was 853.8 (95% CI, 845.7—862.0) and 107.1 (95% CI, 104.3—110.1), respectively (Table 1). Severe CHD represented 11.6% of all CHD cases. The overall prevalence was lower than the summation of the simple CHD and severe CHD because of the coexistence of the two CHD types in the same patient. The most common diseases, in descending order, were VSD (329.9/100,000), ostium secundum-type atrial septal defect (ASDII; 318.0/100,000), patent ductus arteriosus (PDA; 129.5/100,000), pulmonary stenosis (PS; 79.3/100,000), tetralogy of Fallot (TOF; 51.4/100,000), coarctation of aorta (21.4/100,000), endocardial cushion defect (15.6/100,000), and transposition of great arteries (15.5/100,000) (Table 1). These disorders accounted for 35.9%, 34.6%, 14.1%, 8.6%, 5.6%, 2.3%, 1.7%, and 1.7% of the total CHD cases, respectively.

3.2. Gender preference

Although the prevalence of transposition of great arteries (19.8 vs. 10.9), TOF (55.9 vs. 46.5), and aortic stenosis (12.4 vs. 7.6) was higher in boys than in girls, the prevalence of VSD (344.8 vs. 316.2), ASDII (365.1 vs. 277.9), PDA (164.7 vs. 97.1), and endocardial cushion defect (18.3 vs. 13.1) was higher in girls than in boys (Table 1). Moreover, both simple and total CHDs were more prevalent in girls than in boys, and severe CHD was more prevalent in boys.

3.3. Age-specific prevalence in 2010

During infancy, an upward trend was observed for age-specific prevalence of total CHD that was maintained until the age of 3 years, followed by a plateau at 3—10 years. The prevalence rapidly declined to 516.5 per 100,000 children, who reached the age of 14 years, during the following 4 years, i.e., approximately 35.2% of its peak value. The prevalence after the age of 14 years decreased further until adulthood, but at a slower rate. The age-specific prevalence of CHD in 18-year-old individuals was 330.8 per 100,000, approximately 22.5% of the peak value (Figure 1). The prevalence of simple CHD and severe CHD showed the same pattern as total CHD, i.e., a decrease after the age of 10 years. The prevalence of severe CHD decreased to 72.0 at 14 years of age, i.e., approximately 41.8% of its peak value, and further decreased at a slower rate to 53.2 per 100,000 at the age of 18 years, approximately 30.8% of the peak prevalence (Figure 1).

Because the age-specific prevalence of CHD decreased significantly after the age of 10 years, the prevalence of CHD in preschool children aged 0—6 years was also examined (Table 1). In the age group of 6—10 years, the prevalence of CHD was 1233.7 per 100,000, i.e., 1149.6 for simple CHD and 123.5 for severe CHD. Severe CHD represented 10% of all CHD cases. We found that ASDII (477.8 per 100,000 children) was the most common CHD in this age group, followed by VSD (426.1 per 100,000), PDA (153.4 per 100,000), PS (94.4 per 100,000), and TOF (54.9 per 100,000) (Table 1).

3.4. Mortality from CHD in pediatric populations

To elucidate the impact of mortality on disease prevalence, the CHD-specific mortality rate was calculated from the values obtained from the database of Death Statistics in Taiwan. The CHD-specific mortality was 12.9 per 100,000 in children aged 0—5 years; this decreased to 2.7 per 100,000 in the population aged 0—20 years (Table 2). The prevalence of age-specific CHD-related mortality was the highest during infancy (58.8 per 100,000) and declined to 6.2, 2.4, and <1 in children aged 1—2, 2—3, and 3—4 years, respectively. More than 90% (137/157 in 2008 and 124/132 in 2009) of pediatric CHD-related deaths occurred within the first 5 years of life. Among the all-cause mortality, the CHD mortality fraction accounted for 11.7% and 6.6% in children aged 0—5 years and 0—20 years, respectively. For each age group, the highest fraction was found in children aged 0—1 years and 1—2 years (13% deaths in both age

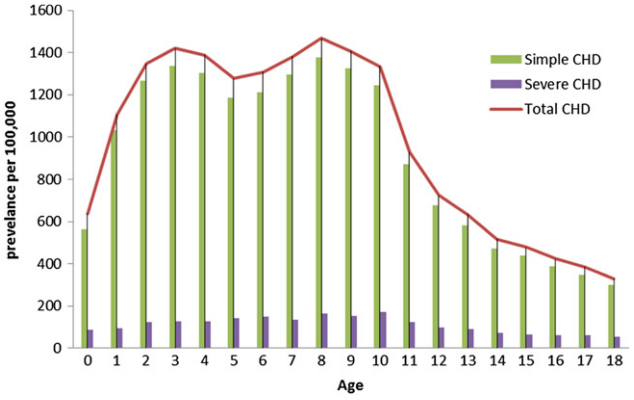

Figure 1 Age-specific prevalence of total, simple, and severe congenital heart diseases (CHDs) (per 100,000 children).

Table 2 The number of deaths from all causes and congenital cardiac anomalies (ICD-10 death codes Q20—Q28) in 2008—2009.

Age (y)	Number of deaths				CHD mortality (10^{-5})	Mortality fraction from CHD*(%)	In an assumed birth cohort	
	All cause	CHD cause					Death probability from CHD† (%)	Cumulative death probability from CHD cause (%)
		Total	Male	Female				
0—1	1675	218	108	110	58.8	13.0	4.50	4.50
2	193	25	9	16	6.2	13.0	0.54	5.05
3	149	10	3	7	2.4	6.7	0.22	5.26
4	115	2	1	1	0.5	1.7	0.04	5.31
5	100	6	2	4	1.4	6.0	0.13	5.44
6—10	432	11	2	9	0.4	2.5	0.24	5.68
11—15	467	6	4	2	0.2	1.3	0.13	5.81
16—20	1242	11	6	5	0.6	0.9	0.24	6.04
0—5	2232	261	123	138	12.9	11.7		
0—20	4373	289	135	154	2.7	6.6		

CHD = congenital heart disease.

* Mortality fraction from CHD cause is a percentage that denotes the number of CHD-related deaths divided by the number of deaths from all causes.

† Death probability from CHD cause was derived by assuming a cohort with a CHD incidence of 1308 per 100,000 and competing risk of death from other causes.

groups). The probability of cardiac death from CHD was the highest during infancy, with a probability of 4.5% that rapidly decreased to 0.54% in children aged 1—2 years and 0.22% in children aged 2—3 years. The probability was quite low after the age of 5 years. The cumulative probability of cardiac death by the ages of 5, 10, 15, and 20 years was 5.44%, 5.68%, 5.81%, and 6.04%, respectively.

4. Discussion

For studying congenital anomalies, both incidence and prevalence are investigated but represent different attributes. Incidence reflects the genetic variation or racial differences involved in diseases, and prevalence reflects the incidence, mortality, and duration of the disease, as well as the disease burden for the society in which it occurs. Although CHD prevalence should be close to its incidence, prevalence may be lower after accounting for mortality and patients lost to follow-up. Based on the information obtained from our national databases, the following two main findings were observed in the present study: (1) the prevalence of pediatric CHD patients who required/received medical care was 918 per 100,000, with a rapid decline after the age of 10 years; and (2) the cumulative probability of death by the time the children were of the age of 10 years and 15 years was 5.68% and 5.81%, respectively. This decline in age-specific prevalence after the age of 10 years is attributed to poor compliance of older children to medical follow-ups rather than to mortality.

The most common types of CHDs were VSD, ASDII, PDA, PS, and TOF, but the incidence and prevalence differed for each CHD group.[9] The prevalent patients had a higher proportion of VSD (35.9% vs. 30.7%), ASDII (34.6% vs. 24.7%), and TOF (5.6% vs. 4.8%) than the neonatal cohort.[10] This difference might be explained by the longer natural history and good survival rate after intervention for these CHDs.[9] However, the proportions of PDA (14.1% vs. 15.4%) and PS (8.6% vs. 9.3%) were high in the neonatal cohort. High spontaneous remission rates and successful interventions at a young age might be the reason for the decreased proportion of both types of CHD in subsequent follow-ups.

As shown in Table 1, although the prevalence of CHD in children aged 0—6 years was found to be 1233 per 100,000 [similar to total CHD incidence (1308 per 100,000)[10]], the overall prevalence of CHDs in children aged 0—18 years was only 918 per 100,000 (i.e., 70.1% of CHD incidence and 74.5% of CHD prevalence in the population aged 0—6 years). Age-specific prevalence decreased dramatically after the age of 10 years. Less than 30% of patients complied with regular cardiac follow-ups up to the age of 18 years, regardless of whether they had simple or severe CHD. Such a change in age-specific prevalence of CHD cannot be explained by the natural or unnatural course of the disease, because the cumulative probability of death in CHD patients from birth to 5, 10, 15, and 20 years of age was only 5.44%, 5.68%, 5.81%, and 6.04%, respectively. In addition, there are 19 medical centers in Taiwan providing pediatric cardiac programs under almost full NHI coverage; medical access for CHD care is easy. Therefore, the lack of willingness to attend continual cardiac follow-up after entering school seems to be the major reason for the decline in age-specific prevalence. Similar trends have been observed in previous longitudinal follow-up studies.[17—19] Mackie et al[19] reported that the compliance rate for continual cardiac follow-up was only 72% at 6—12 years and 53% at 13—17 years in CHD patients who were diagnosed before the age of 6 years.[19] Male patients and those with less severe CHD are less likely to pursue follow-up care.[19] Despite this factor, the noncompliance rate is very high in Taiwan, the reasons for which should be investigated in the future. Such low adherence might cause unnecessary complications such as bacterial endocarditis, hyperviscosity syndrome, and iron deficiency anemia; these complications result in increased morbidity, subsequent

mortality, and disease burden in children with CHD as they grow up.

Infant mortality in Taiwan is similar to that in the United States.[9,13] Of all infant deaths, congenital malformations, deformations, and chromosomal anomalies (ICD 10, Q00—Q99) are the leading causes in both the United States and Taiwan, accounting for 19.9% (United States) and 22.8% (Taiwan).[20] CHD-related infant mortality in Taiwan was approximately 58.8 per 100,000, which was higher than that in the United States (41.46 per 100,000).[3] The difference in CHD-related infant mortality between these two countries in the age group of 1—5 years was still significant (2.59 and 1.38 per 100,000 in Taiwan and the United States, respectively). In the age group of 6—15 (17) years, the differences became insignificant (0.30 vs. 0.41 per 100,000). Overall, the CHD-related mortality rate in U.S. infants was only 71% of the Taiwanese rate; in preschool children, it was only 53%. Because the incidence of severe CHD is approximately 1.5/1000 in both Taiwan and the United States,[9] worse outcomes of CHD infants and children in Taiwan should not be related to disease severity *per se*. This should be clarified by further outcome-based studies.

In summary, the prevalence of CHD in pediatric patients who required/received medical care in Taiwan was 918 per 100,000 for individuals aged 0—18 years and 1233 per 100,000 for children aged 0—6 years. Because most (i.e., greater than 90%) of CHD deaths occurred within the first 5 years of life (mainly during infancy), the decline in the age-specific prevalence of CHD after the age of 10 years was attributed to noncompliance to medical follow-ups because of the interference of schooling activity. Even in countries with a national health insurance system and easy medical access, poor compliance to medical follow-ups is a common phenomenon in CHD children of school-going age.

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