Pediatric Cardiology

Coronary Artery Complications in Pediatric Patients with Kawasaki Disease: A 12-Year National Survey

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Background: Coronary artery complications are the predominant causes of morbidity and mortality in childhood Kawasaki disease (KD). The aim of this study was to investigate the incidence of coronary artery complications and cardiac sequelae in pediatric patients with KD.

Methods: Using the Taiwan National Health Insurance (NHI) database from 1997 to 2008, records of patients with KD were reviewed retrospectively, utilizing the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 446.1 in pediatric patients aged 18 years or under. The ICD-9CM was also used to identify the outcomes for coronary artery complications (ICD-9-CM codes 410-414), including coronary artery aneurysm (CAA) (ICD-9-CM code 414.11).

Results: From the records of pediatric patients with KD admitted to hospitals between 1997 and 2004, 8148 patients without any history of coronary artery complications before KD were selected for study. Of those patients, 694 patients (8.5%) were followed-up until the end of 2008 to estimate the incidence of coronary artery complications. The ratio of boys to girls with coronary artery complications was 1.84, and the incidence of coronary artery complications was 11.53 per 1,000 person-years. Among the 8148 pediatric patients with KD, 12 patients (0.15%; 8 boys and 4 girls) had myocardial infarction, and 20 patients (0.25%; 12 boys and 8 girls) died during follow-up.

Conclusions: This study is the first report regarding the incidence of coronary artery complications in KD children aged 18 years or younger. The incidence of coronary artery complications was higher as patients progressed in age, and increased by year. However, major complications such as death and myocardial infarction did not frequently occur.

Key Words: Cardiac sequelae • Coronary artery complications • Incidence • Kawasaki disease

INTRODUCTION

Kawasaki disease (KD) is an acquired vasculitis of unknown etiology, though over 40 years have passed since Dr. Tomisaku Kawasaki initially reported the first series of KD cases.[1] KD is probably induced by infection and has seasonality.[2] Typically, KD presents in children younger than 5 years of age as a febrile illness with mucocutaneous changes. Coronary artery complications in children with KD, such as coronary artery aneurysm (CAA), are one of the most important aspects of this disease. CAA produces artery remodeling over time, leading to coronary artery disease.[3] Some patients develop myocardial infarction or heart failure, or even death.[4-6] For children in developed countries, KD is known as the leading cause of acquired heart disease.[7,8]

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A case series of 594 children with KD during 10 to 21 years of follow-up showed CAA developed in 25% of untreated children; during follow-up, ischemic heart disease developed in 4.7%, myocardial infarction, in 1.9%, and death occurred in 0.8%.[6] Another recent case series of 261 young adults < 40 years of age undergoing angiography for myocardial ischemia showed that coronary sequelae of KD were present in 5% the young adults.[9] An earlier school-based mass survey of children with KD in Taiwan from 1976 to 2000 showed the highest incidence of 54.9 per 100,000 children < 5 years of age in 1998.[10] Coronary artery lesions were noted during the acute, subacute, and convalescent stages of KD in 25.8% of children aged 6 to 18 years. In a nationwide survey of Taiwan's national health insurance (NHI) database from 2003 to 2006, Taiwan had the third highest global incidence of KD after Japan and Korea, with 69/100,000 children younger than 5 years of age.[11] Of these children, 90% were < 5 years of age, and the male/female ratio was 1.62:1. Additionally, 7.2% of these children developed CAA and the incidence of CAA was higher in boys. The newest nationwide report of KD in Japan shows that the incidence and number of patients with KD continue to increase. Of these children, 9.3% had coronary artery complications during acute KD, and 3.1% had cardiac sequelae 1 month after onset of KD. The cardiac sequelae were highest among infants and children older than 5 years of age.[12] In some areas or countries with low KD incidence, the proportion of coronary artery complications ranged from 2.3%-5%.[13-15]

Coronary artery complications are of critical importance for patients with KD. During the era of intravenous immunoglobulin (IVIG) therapy for acute KD, it is standard therapy for patients with KD to receive IVIG. It has been observed that such IVIG therapy can reduce the incidence of CAA in KD.[16] The incidence of coronary artery complications among KD patients in Taiwan has not been well investigated. Therefore, we investigated the incidence of coronary artery complications in Taiwanese children with KD. Secondly, we followed up on the cardiac sequelae of these children using Taiwan's national health insurance (NHI) database for the period of 1997-2008. The NHI database is a good source of nationwide data because it encompasses most of the medical care costs of more than 99% of the Taiwanese population.[17] We chose 1997 as the starting period for selection of KD cases with coronary artery complications. It was assumed that children with KD would be admitted to the hospital when they had coronary complications, and so we opted to use the hospitalization database of Taiwan's NHI. We selected cases from within the 1997 to 2004 time period, and all children were monitored through 2008.

METHODS

Database and patient identification

Eight years of population-based data (1997-2004) from the NHI database of inpatient expenditures for hospital admissions were examined to determine the incidence rates of coronary artery complications in KD pediatric patients. Pediatric patients with a history of coronary artery complications prior to diagnosis of KD were excluded. All disease records were selected according to one principal diagnosis (KD), and up to four secondary diagnoses as coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM). The ICD-9CD code for KD is 446.1. Coronary artery complications in the ICD-9CD codes are defined as a listing of any of the following disease codes: acute myocardial infarction (MI; ICD-9-CM code 410), other acute and subacute forms of ischemic heart disease (IHD; ICD-9-CM code 411), old myocardial infarction (ICD-9-CM code 412), angina pectoris (ICD-9-CM code 413), other chronic ischemic heart disease (IHD; ICD-9-CM code 414), and CAA (ICD-9-CM code 414.11). Pediatric patients with KD were diagnosed to have coronary artery complications when they had for the first time any of the listed disease codes during the follow-up period. All of the pediatric patient records were from children aged 18 years or younger. These KD pediatric patients were analyzed by age, gender, geographic region of hospitalization, and urbanization. The level of urbanization of Taiwan townships was based on the Liu et al. paper, including measurement of index variables of population density, ratios of educational levels of people with college education or above, ratio of elderly people (> 65 years of age), ratio of people employed as agriculture workers, and the number of physicians per 100,000 people.[18] The study period ranged from 1997 to 2008, so the follow-up time could have been up to 12 years.

Statistical analysis

The data are expressed as mean (± standard deviation) and frequencies (percentages). The mean differences of continuous variables (age) between boys and girls were compared using the Student's *t*-test. Pearson's chi-square test was used to compare discrete variables such as age groups, geographic regions, urbanization, and outcomes (death and coronary artery complications) between boys and girls. The incidence of coronary artery complications in KD pediatric patients was calculated from a count of pediatric patients with coronary artery complications divided by the total number of person-years. The Poisson regression with total person-time as an offset variable was applied to analyze the statistical differences between boys and girls. The linear trend test was applied to examine the upward or downward trend in incidence rate. p values < 0.05 were defined as statistically significant, and statistical Analysis System (SAS) software (version 9.2; SAS Institute, Inc., Cary, NC, USA), was used to perform all statistical analyses.

RESULTS

Table 1 shows the demographic data of all pediatric children with KD based on Taiwan's NHI database for the time period 1997 to 2004. The records of 8148 pediatric patients with KD, but without a history of coronary ar-

Table 1. Demographic information for pediatric patients with Kawasaki disease, from 1997-2004

	Total (N = 8148)	Female (N = 3110)	Male (N = 5038)	p value*
Age (mean ± SE)	2.16 ± 0.02	2.16 ± 0.04	2.16 ± 0.03	0.99
Age (%)				
< 1	2974 (36.50)	1068 (34.34)	1906 (37.83)	0.002
1-2	2145 (26.33)	871 (28.01)	1274 (25.29)	
2-3	1173 (14.40)	483 (15.53)	690 (13.70)	
3-4	672 (8.25)	242 (7.78)	430 (8.54)	
4-5	439 (5.39)	158 (5.08)	281 (5.58)	
≥ 5	745 (9.14)	288 (9.26)	457 (9.07)	
Urbanization (%)				
1	3935 (48.36)	1479 (47.60)	2456 (48.83)	0.07
2	3509 (43.12)	1348 (43.39)	2161 (42.96)	
3	256 (3.15)	118 (3.80)	138 (2.74)	
4	391 (4.81)	142 (4.57)	249 (4.95)	
5	46 (0.57)	20 (0.64)	26 (0.52)	
Coronary complications (%)‡				
Overall	694 (8.52)	244 (7.85)	450 (8.93)	0.09
MI	9 (1.30)	3 (1.23)	6 (1.33)	0.86
IHD only	71 (10.23)	28 (11.48)	43 (9.56)	
IHD with MI	1 (0.14)	0 (0.00)	1 (0.22)	
CAA only	611 (88.04)	212 (86.89)	399 (88.67)	
CAA with MI	2 (0.29)	1 (0.41)	1 (0.22)	
All CAA (%)				
Yes	620 (7.61)	215 (6.91)	405 (8.04)	0.06
No	7528 (92.39)	2895 (93.09)	4633 (91.96)	

CAA, coronary artery aneurysm; IHD, ischemic heart disease; MI, myocardial infarction.

* p value was calculated using Student's *t*-test for continuous variables and the chi-square test was used for categorical variables; There were 11 observations without urbanization information; ‡ Coronary complications were defined as KD pediatric patients were diagnosed to have any the following diseases of MI, IHD or CAA at the first time during the follow-up period. IHD with MI indicated the patient had the diagnosis of IHD and MI at the same hospitalization. CAA with MI indicated the patients had the diagnosis of CAA and MI at the same hospitalization.

Note: There are 7 urbanization levels in Taiwan: level 1, the most urbanized, to level 7, the least urbanized. Since there were very little data for levels 5, 6, and 7, these 3 levels were combined into a single group, level 5 in the table.

tery complications, were selected for follow-up.

The average age at onset of KD was 2.16 ± 0.02 years. Over 90% of the pediatric patients with KD were under the age of 5, with a peak age of less than one year old. There was no difference in the incidence of KD by geographic region or urbanization. All pediatric patients with KD were monitored up to 2008, and 694 pediatric (8.52%) patients with KD were diagnosed with coronary artery complications, which included 620 subjects (7.61%) with CAA. The proportion of CAA as a proportion of overall coronary complications was 89.3%.

Incidence of coronary artery complications for KD pediatric patients

The overall incidence of coronary artery complications among pediatric patients with KD from 1997 through 2004 was 11.53 per 1000 person-years (Table 2). Almost twice as many boys than girls had coronary artery complications (boys:girls, 1.84).The gender difference in incidence of coronary artery complications among children with KD from 1997 through 2004 was 1.14 (boys: 12.12 per 1000 person-years; girls: 10.60 per 1000 person-years). The overall incidence of CAA from 1997 through 2004 was 10.20 per 1000 person-years. The gender difference in incidence of coronary artery aneurysms among pediatric patients with KD from 1997 through 2004 was 1.17 (boys: 10.79 per 1000 person-years, girls: 9.24 per 1000 person-years). The incidences of coronary artery complications were higher among older patients (Table 2). The highest incidence of coronary artery complications occurred at the age of 5 or older, with 15.83 per 1000 person-years. Coronary artery complications were more common at the age of 5 or older (11.28%). The incidences of coronary artery complications in pediatric patients with KD ranged from 7.17 per 1000 person years in 1997 to 14.55 per 1000 person-years in 2004 (Figure 1). The incidences of coronary artery complications in pediatric patients with KD increased year by year. Boys had higher incidences of coronary artery complications than girls did at the age of 3 years or younger (Figure 2, p = 0.05). Boys also had a higher incidence of CAA than girls did at the age of 3

Table 2. Incidence of coronary artery complications in pediatric patients with Kawasaki disease

	Kawasaki disease (N = 8148)			
	Total N	N (%)	Person-years	Rate*
Coronary artery complications	8148	694 (8.52)	60149.93	11.54
Gender				
Male	5038	450 (8.93)	37136.56	12.12
Female	3110	244 (7.85)	23013.36	10.60
Age, years				
< 1	2974	245 (8.24)	22268.77	11.00
1-2	2145	162 (7.55)	15941.86	10.16
2-3	1173	97 (8.27)	8653.83	11.21
3-4	672	60 (8.93)	4817.13	12.46
4-5	439	46 (10.48)	3161.14	14.55
≥ 5	745	84 (11.28)	5307.20	15.83
Coronary artery aneurysm	8148	620 (7.61)	60801.88	10.20
Gender				
Male	5038	405 (8.04)	37528.11	10.79
Female	3110	215 (6.91)	23273.76	9.24
Age				
< 1	2974	225 (7.57)	22450.50	10.02
1-2	2145	147 (6.85)	16052.34	9.16
2-3	1173	85 (7.25)	8771.92	9.69
3-4	672	57 (8.48)	4847.27	11.76
4-5	439	43 (9.79)	3192.26	13.47
≥ 5	745	63 (8.46)	5487.58	11.48

* Rate: per 1000 person-years.

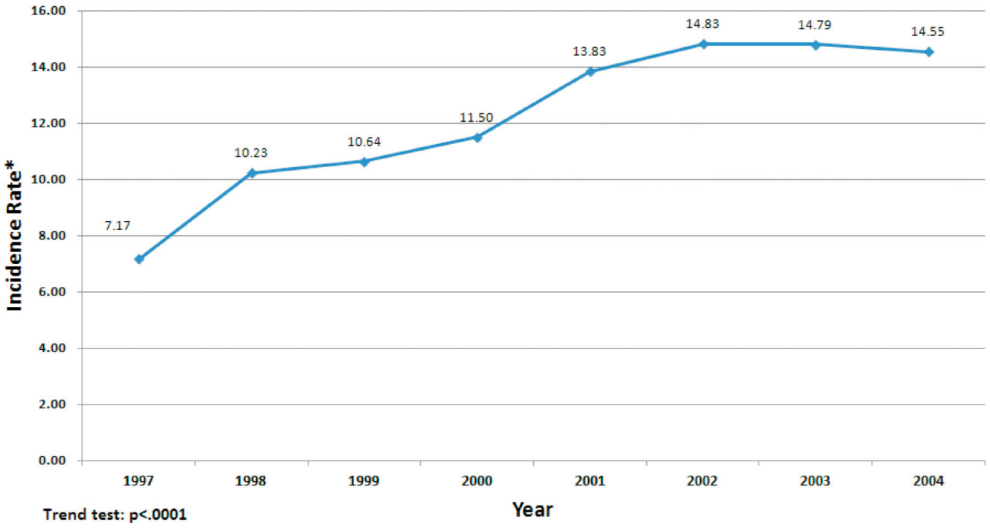


Figure 1. *The incidence of coronary artery complications in pediatric patients with Kawasaki disease (KD) by year from 1997 to 2004.*

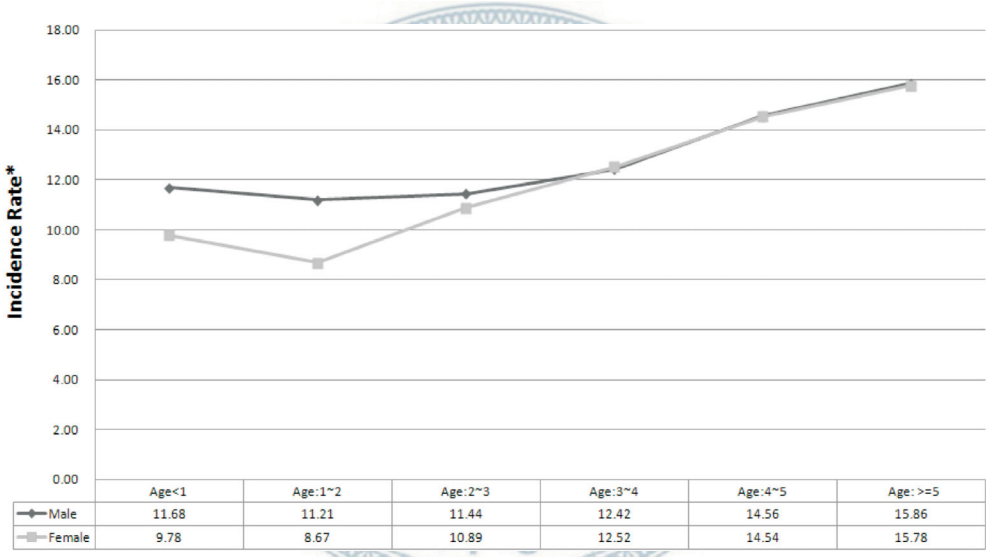


Figure 2. *The incidence of coronary artery complications in pediatric patients with Kawasaki disease (KD) by gender from 1997 to 2004. (Incidence Rate*: per 1000 person-years)*

years or younger (Figure 3, p = 0.03).

Follow up of coronary artery complications for KD pediatric patients

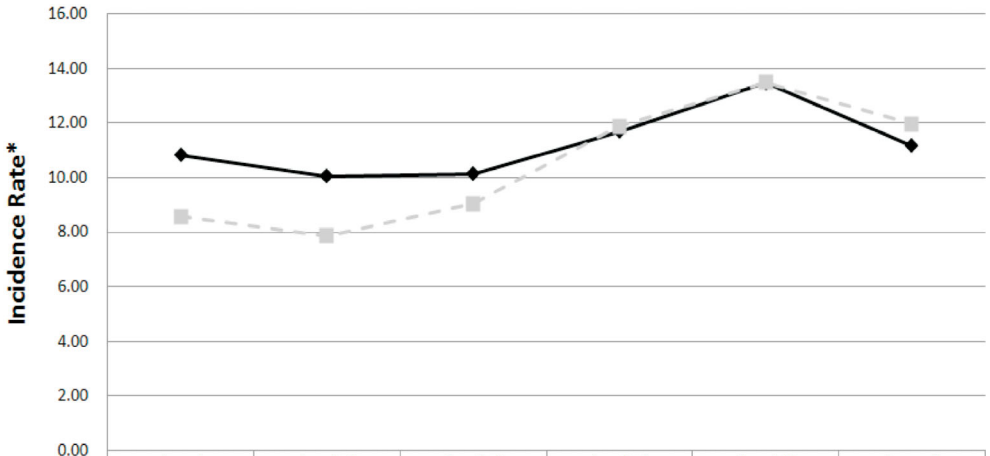
Arising from our targeted patients in the NHI database from 1997 through 2008, some 8148 pediatric patients with KD had a median follow-up of 7.7 years (interquartile range, 5.6-9.8) with a maximum follow-up time of 12 years. A total of 694 subjects (8.52%) with KD had coronary artery complications were followed until the end of 2008. Over 90% of pediatric patients with KD were diagnosed with coronary artery complications within 1 month of onset of KD. The average time to the development of coronary artery complications in pediatric patients with KD was 2.36 ± 11.63 months. There was no difference in gender (girls, 2.03 ± 12.07 months; boys, 2.54 ± 11.39 months, p = 0.58). There were 38 pediatric patients (5.48%) readmitted to the hospital, with no noted difference in gender upon readmission (girls, 5.74% and boys, 5.33%). The Kaplan-Meier coronary artery complication-free curve of the entire cohort of KD patients is shown in Figure 4. Although not statistically significant, the trend was still compatible with the finding of a higher risk of developing coronary artery com-

plications in boys than in girls when children with KD were 3 years of age or younger (p = 0.06). In addition, when comparing the older and younger children (age > 3 vs. age ≦ 3), the risk ratio for coronary artery complications is 1.33 (95% CI: 1.12-1.57, p = 0.0008).

Of the 8148 pediatric patients with KD, 620 (7.61%) had CAA during the follow-up period. The average time to development of CAA in KD patients was 2.35 ± 11.73 months. There was no difference in gender (girls, 2.15 ± 12.79 months; boys, 2.45 ± 11.14 months, p = 0.77). Of all CAA pediatric patients, 35 (5.65%) pediatric patients were readmitted to the hospital. There was no difference in gender among readmitted pediatric patients (girls, 6.05%; boys, 5.43%). The Kaplan-Meier CAA-free curve of the entire cohort of pediatric patients with KD is shown in Figure 5. When KD pediatric patients were younger than 3 years of age, boys had a higher risk of developing CAA than girls did (p = 0.03). The risk ratio of coronary artery aneurysm is 1.25 (95% CI: 1.04-1.49, p = 0.02) between older age and younger children.

Cardiac sequelae

During the follow-up period of 1997 to 2008, MIs and deaths among the 8148 pediatric patients with KD were rare, with only 0.15% MIs (boys, 8; girls,4) and 0.25% deaths (boys, 12; girls, 8). In addition, only two



	Age<1	Age:1~2	Age:2~3	Age:3~4	Age:4~5	Age:>=5
Male	10.84	10.06	10.15	11.69	13.46	11.18
Female	8.57	7.87	9.05	11.88	13.49	11.97

Figure 3. *The incidence of coronary artery aneurysm (CAA) in pediatric patients with Kawasaki disease (KD) by gender from 1997 to 2004. (Incidence Rate*: per 1000 person-years)*

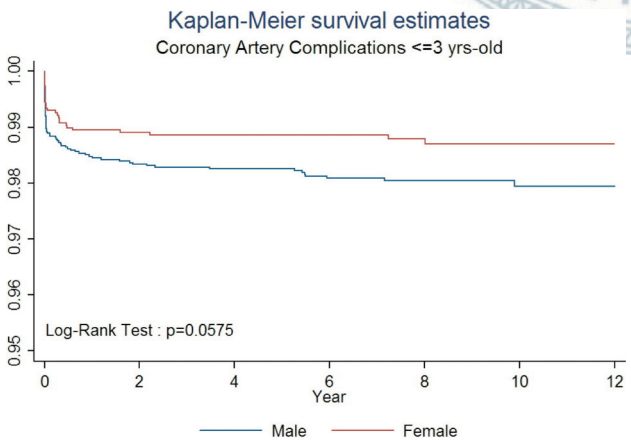


Figure 4. *Twelve-year event-free follow-up of coronary artery complications in children ≤ 3 years of age with Kawasaki disease (KD) by gender.*

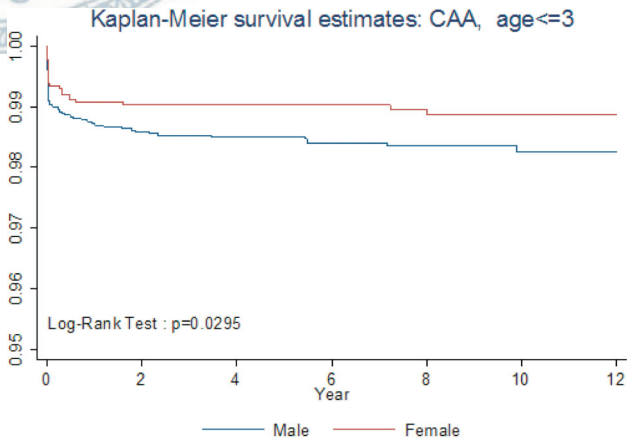


Figure 5. *Twelve-year event-free follow-up of coronary artery aneurysm (CAA) in children ≤ 3 years of age with Kawasaki disease by gender.*

pediatric patients with KD received percutaneous coronary angioplasty. Twenty KD pediatric patients died during follow-up and the average time from the diagnosis of KD to death was 2.00 ± 2.50 years. The events of MI and death did not differ by sex. Among the 620 KD patients with CAA, 5 pediatric patients (0.8%) died and 3 pediatric patients (0.5%) had MIs during follow-up (Table 3). Of the 7528 KD pediatric patients without CAA, 15 pediatric patients (0.2%) died and 9 pediatric patients (0.1%) had MIs.

Table 3. The distribution in pediatric patients with KD between with CAA and without CAA for MI and death

	KD with CAA (N = 620)	KD without CAA (N = 7528)	p value*
MI			
Yes	3 (0.48)	9 (0.12)	0.06
No	617 (99.52)	7519 (99.88)	
Death			
Yes	5 (0.81)	15 (0.20)	0.01
No	615 (99.19)	7513 (99.80)	

* Fisher's exact test.

DISCUSSION

We describe the epidemiologic features and trends of coronary complications in KD in Taiwan using the Taiwan NHI database from 1997 to 2008. To the best of our knowledge, our study was the first report of the incidence of coronary artery complications in pediatric patients with KD aged 18 years or younger. The male-to-female ratio among pediatric patients with KD was 1.62 and the percentage of CAA was 7.61%. Almost twice as many boys as girls had coronary artery complications (boys:girls = 1.84). A previous nationwide survey of Taiwan's NHI database during 2003-2006 showed the male-to-female ratio of KD children was also 1.62 and the incidence of CAA was 7.2%.[11] The two KD study populations had very similar basic characteristics.

The incidence of coronary complications for subjects with KD gradually increased from 1997 to 2004. It is difficult to distinguish between increased case ascertainment and a true increase in the number of affected children. The proportion of coronary artery complications for children with KD in our survey was 8.52%. From the earlier survey of KD in Taiwan, the epidemiological features of KD in Taiwan were similar to those in Japan.[10] However, the proportion of cardiac sequelae in KD in the 2009-2010 Japan nationwide survey was 3%, and the proportion of cardiac lesions in the acute phase in KD was 9.3%.[12] One possible reason for this difference is that our coronary artery complications included acute cardiac lesions that developed within 1 month of onset of KD and cardiac sequelae of KD persisting beyond 1 month after onset of KD. Thus, most KD patients in Taiwan developed coronary complications within 1 month of onset. The incidence of coronary complications in our study may reflect the most acute phase of coronary complications for KD patients. In addition, the current knowledge of KD and advancement of diagnostic techniques and imaging led us to diagnose coronary complications easier and faster. Thus, the number of children with coronary artery complications increases in the acute phase of KD.

The proportion of coronary artery complications in our children with KD was the highest at the age of 5 years old or older, even in the acute stage, which differs from the Japanese experience, although the epidemiological features of Kawasaki disease in Taiwan are similar to those in Japan. The 2009-2010 nationwide survey in Japan showed the prevalence of cardiac lesions in the acute phase, and cardiac sequelae were highest among infants and older children.[12] We found that the incidence trends of coronary artery complications and CAA in KD were higher in boys at the age of 3 years or younger. In a previous nationwide survey of KD in Taiwan, boys had a higher incidence of CAA than girls did, but no further age analysis by gender was done.[11] In a recent survey of the Taiwan NHI database for coronary risks of KD at ages < 40 years, the risk of coronary complications was highest from birth to 5 years of age and higher in males; the male-to-female ratio was greater than 2 for all patients older than 20 years of age.[19] The majority of hospitalizations for KD occurred among children < 3 years of age from 1997 to 2007 in the United States and more boys than girls were hospitalized.[20] These results also suggest that the risk of coronary complication is greater in boys < 3 years of age in the United States.

CAA (89.3%) was the predominant coronary artery complication in our study. The rate of CAA in our children with KD was 7.61%. In a case series consisting of 74

patients with KD, CAA was the most common cardiac complication (93.2%).[21] In Beijing, 20.6% of children with acute KD have CAAs, including dilatations and aneurysms.[22] In Korea, the proportion of coronary artery lesions in children with KD was 17.5% during 2006-2008.[23] In our study, the average duration from onset of KD to development of CAA was 2.35 ± 11.73 months. Thus, it seems reasonable to monitor children with KD closely for at least 1 year after diagnosis.

In the previous survey of KD in Taiwan, 1.5% patients with KD had recurrence.[11] In a recent national survey in Japan, the recurrent rate was about 3.6%.[12] In our study, 5.48% of pediatric patients with coronary artery complications were hospitalized again during follow-up.

Mortality among children with KD was 0.15% in our study, which is close to the 0.17% reported in an American study using a hospitalization database,[20] but higher than 0.08% as reported in a Japanese study.[25] Although we could see that deaths had occurred in our database, we did not know the true cause of death. Mortality in our study was defined as mortality at discharge. In addition, our data showed lower incidences of death and MI in pediatric patients with KD but without CAA, compared to children with KD and CAA for the 12-year follow-up duration. A cases series of 76 patients with KD with giant coronary aneurysm after 19 years of follow-up showed survival rates at 10, 20, and 30 years after the onset of KD were 95%, 88%, and 88%, respectively.[26] Our results also showed low mortality and morbidity among children with CAA during the 12-year follow-up study, and its course was not malignant.

There are some limitations to the study. The maximum long-term follow-up duration for cardiac sequelae outcomes was only 12-years, according to Taiwan's NHI database. We did not explore the factors of the seasonal variation or geographical distribution. Additionally, the relationship between urbanization and incidence of cardiac sequelae deserves further investigation. The cardiac sequelae in our study did not include rare heart valve disease or myocarditis. We did not identify the severity of coronary complications and the reason of death in pediatric patients with KD in the database. In addition, we could not identify giant CAA, incomplete CAA, or CAA regression in the database, nor could we determine how long the cardiac sequelae persisted.

CONCLUSION

The incidence of coronary artery complications in our pediatric patients with KD was 11.53 per 1,000 person-years. The incidence was higher for older ages and increased by year. In addition, boys three years of age or younger had a higher risk and incidence of CAA than girls. However, major complications, such as death and MI, did not occur frequently.

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