Prevalence and the Long-term Coronary Risks of Patients With Kawasaki Disease in a General Population <40 Years
A National Database Study

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Background—Patients with Kawasaki disease (kDa) may develop coronary arterial lesions and subsequent coronary events. The first reported case in Taiwan was in 1976, and the annual incidence from 2003 to 2006 was 69/100 000 children <5 years. A population study from Taiwan, a country with a high incidence of kDa, national health insurance, and easily accessible medical care, would adequately reflect the long-term risk.

Methods and Results—We retrieved the data of kDa patients from a national health insurance 2000 to 2010 database of Taiwan, a country with a child health index similar to those in the United States. The occurrence of coronary complications and interventions was identified by the respective International Classification of Diseases, Ninth Revision, codes. The prevalence of kDa in the population <40 years was 34.9/100 000 (male/female ratio, 1.47). Coronary complications occurred in 1254 patients (5.37%; male/female ratio, 2.19), with an average annual risk of 2.4% (2.7% for males and 2.0% for females). An acute myocardial infarction occurred in 19 patients (0.08%; 18 males and 1 female), of whom one third were aged between 10 and 15 years (median, 15.7 years; range, 0.7–36.7 years). A coronary intervention was performed by catheterization in 18 patients (all males) at a median age of 24.5 years and by surgery in 10 patients (male/female ratio, 4.0) at a median age of 21.7 years, with mortality at discharge being 0% and 25%, respectively.

Conclusions—This study estimated the overall prevalence of kDa (=1/2940) in a population <40 years. They, particularly the males, carry long-term coronary risks from a young age. Risk stratification for a timely coronary intervention and risk modification are mandatory. (Circ Cardiovasc Qual Outcomes. 2012;5:566-570.)

Key Words: Kawasaki disease ■ prevalence ■ myocardial ischemia ■ acute myocardial infarction ■ coronary intervention ■ coronary artery bypass

Kawasaki disease (kDa) is the most common form of pediatric systemic vasculitis, and occurs predominantly in children <5 years.1,2 The first patient report was by Dr. Kawasaki in 1967; thereafter, the incidence showed a trend of increasing every year.3-7 There are also strong racial differences, with a higher incidence in Asians than in Western populations.5-7 Coronary arterial lesions (CALs) occur in an estimated 5% to 15% of kDa patients during the acute stage,3-7 and late CAL may persist and even progress to stenosis or obstruction.2,7 Kawasaki disease is the leading cause of acquired heart disease in children. Myocardial ischemia or acute myocardial infarction (AMI) may occur during the acute stage and subsequent follow-up.3,4,6-10 However, information regarding the long-term coronary risk from CAL in kDa patients is limited.

In Taiwan, after the first reported case of kDa in 1976, the number of kDa patients increased steadily until 2000.3,4 From 2003 to 2006, the incidence of kDa in Taiwan was 69/100 000 children <5 years: the only countries with a higher incidence were Japan (218/100 000) and Korea (113/100 000).4,7 The population of Taiwan is ≈23 million people, with 21% of them being the pediatric population (<18 years old). The national health insurance (NHI) program was started in 1995 and covered >98% of the general population. The health care system in Taiwan is regarded as sound, and the child health index is similar to that in the United States.11 We hypothesized that the number of patients with kDa and the related coronary complications in Taiwan, a country with a high incidence of kDa and full and easily accessible medical care, would adequately reflect the long-term risk from CAL among kDa patients. We used the national database from Taiwan’s NHI system to explore the prevalence of kDa and the associated risk from coronary complications in the general population <40 years. The coronary complications that
we investigated included myocardial ischemia and the relevant interventions.

WHAT IS KNOWN

- Coronary arterial lesions develop in 5% to 15% of patients in the acute stage of Kawasaki disease (kDa), which is the most common form of pediatric systemic vasculitis.
- These coronary arterial lesions may persist and progress into stenoses, sometimes resulting in myocardial ischemia or infarction.
- In Taiwan, after the first reported case of kDa in 1976, the incidence of kDa was 69/100 000 children <5 years: the only countries with a higher incidence were Japan (218/100 000) and Korea (113/100 000).

WHAT THE STUDY ADDS

- To our knowledge, this study was the first to investigate the prevalence and long-term coronary risk in patients with kDa using a nationwide Taiwanese database (representing >98% of the general population spanning 11 years).
- We found that the prevalence of kDa was 34.9/100 000 in those aged <40 years, and the annual coronary risk was 2.4%.
- An AMI occurred in 19 patients (18 males and 1 female) at a median age 15.7 years. The chance of coronary intervention in kDa patients, although still low, was much higher than that in the general population. Patients with kDa, particularly males, carry long-term coronary risks from a young age.

Methods

NHI Database and Patient Identification

All health care records logged between January 1, 2000, and December 31, 2010, were retrieved from the complete computerized database of the NHI. Patients aged <40 years and diagnosed as having kDa (code 446.1), according to the criteria listed in the International Classification of Diseases, Ninth Revision, Clinical Modification, were selected. Each health record had a scrambled identification number and contained information such as the patient’s date of birth, date of hospital visit, sex, type of visit (admission or outpatient department visit), diagnosis and treatment codes, and reimbursement fees. To estimate kDa prevalence, we defined patients as those admitted to a hospital with the major diagnosis of kDa or those who visited the outpatient department with the major diagnosis of kDa. The overall prevalence and age-specific prevalence (per 100 000 persons) were calculated from the sex-specific population sizes between 2000 and 2010 by 5-year age categories.

Definition of Coronary Complications, Cardiac Catheterization, and Interventions

Identified patients were tracked for any complications or interventions (defined later) until December 31, 2010. The occurrence of coronary complications was defined as a listing of any of the following disease codes for first or second diagnosis: 410 (AMI), 412 (old myocardial infarction), 413 (angina pectoris), or 414 (other forms of chronic ischemic heart disease). Cardiac catheterization was defined by reimbursement for any of the following treatment codes: 18020B, 18021B, 18022A, 18022B, 18027B, 97501K, 97502A, 97502B.

Results

Overall and Age-Specific Prevalence of kDa

The average population of individuals <40 years during the 11-year study period was 13 378 830. The overall prevalence of kDa in this population group was 34.9/100 000 (23 349 patients; male/female ratio, 1.47). The age-specific prevalence was highest in the age group from birth to 5 years (164.6/100 000), followed by 5 to 10 years (109.5/100 000). The prevalence decreased rapidly for patients in the age group 10 to 15 years; the prevalence was low after the age of 20 years and rare after the age of 25 years. Male predominance was noted in all age groups (Figure 1).

Risk of Coronary Complications and Coronary Interventions

Among the 23 349 kDa patients identified from the database, 1254 (5.37%) had coronary complications (861 males and 393 females; male/female ratio, 2.19). The average annual risk of coronary complications was 2.4% (2.7% in males and 2.0% in females). The risk was highest in the age group from birth to 5 years (3.7%), followed by 35 to 40 years (2.7%), 30

Figure 1. The prevalence of Kawasaki disease in each age male and female group from the National Health Insurance Database 2000 to 2010 from Taiwan.

97503, 97506K, 97507A, or 97508B. Percutaneous coronary intervention (PCI) was defined by reimbursement for any of the following treatment codes: 33076B, 33077B, 33078B, 97511K, 97512A, 97513A, 97513B, 97516K, 97517A, 97518B, 97521K, 97522A, and 97523B. Surgical coronary artery bypass grafting (CABG) was defined by reimbursement for any of the following treatment codes: 68023A, 68023B, 68024A, 68024B, 68025A, 83064A1, 97901K, 97902A, 97902A, 97903B, 97906K, 97907A, 97908B, 97911K, 97912A, 97913B, 97916K, 97917A, and 97918B. The annual risk for various coronary complications was calculated as an average for 2000 to 2010; this figure was obtained by dividing the number of cases with complications by the total number of kDa patients. Acute mortality was defined as the event of death occurring at discharge.

Statistics

We used SAS 9.2 software (SAS; Cary, NC) to perform the statistical analyses. The overall prevalence and age-specific prevalence (5-year age categories) were calculated from the sex-specific population sizes between 2000 and 2010, which were adopted from the Statistical Yearbook of Interior, Department of Statistics, Ministry of Interior.12
to 35 years (2.7%), and 20 to 25 years (2.4%). The risk of coronary complications was higher for male than female patients, and the male/female ratio was > 2 for all patients > 20 years (Figure 2). Admission for AMI was noted in 19 patients (18 males and 1 female), with a total of 21 admissions: 0.08% (19/23,109) of the whole kDa group and 1.52% (19/1,254) of kDa patients with coronary complications. Patient’s age at admission ranged from 0.7 to 36.7 years (median, 15.7 years; 20.1±11.8 years). The age distribution at admission is shown in the Table. Most AMI episodes (7 [33%] of 21) occurred in the age group 10 to 15 years. There was no mortality at discharge among patients admitted for AMI.

A total of 393 cardiac catheterization procedures were performed in 316 patients (232 males and 84 females; male to female ratio, 2.71) at a median age of 6.6 years (8.6±7.3 years) (Table). Among them, 18 patients (all male) received PCI at a median age of 24.5 years (22.8±12.1 years). This subgroup represented 0.078% of the whole kDa group (18/23,109) and 1.44% of kDa patients with coronary complications (18/1,254). In addition, 10 patients (male/female ratio, 4.0), representing 0.043% of cases in the whole kDa group (10/23,109), underwent CABG at a median age of 21.7 years (21.3±12.1); the same subgroup represented 0.80% of the kDa patients with coronary complications (10/1,254). The rate of acute mortality (defined as mortality at discharge) was 0% (0/18) for PCI patients and 25% (4/16) for CABG patients.

### Discussion

Patients with kDa are at increased risk of coronary events. To our knowledge, this study was the first to investigate the prevalence and long-term risk of coronary complications in kDa patients using a nationwide database (representing >98% of the general Taiwanese population for >11 years). Our main findings were as follows: (1) in the general population < 40 years, the prevalence of kDa was 34.9/100,000; (2) the annual risk of coronary complications in kDa patients was 2.4%; (3) coronary intervention was performed by PCI in 1.44% and by surgery in 0.80% of patients who had coronary complications; and (4) among patients with coronary complications, AMI occurred in 1.52% of cases. Probably because of improved disease recognition or other environmental influences, the reported incidence of kDa has been increasing with each passing year in many countries.4–7 In Taiwan, an island country with a population of 23 million, this trend of increase was clearly evident until 2000.4,5 Since 2000, the annual kDa incidence among children < 5 years has ranged from 60/100,000 to 70/100,000.4,5 However, prevalence data

### Table. Age Distribution of the Age at Admission for Cardiac Catheterization, PCI, or CABG

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age Group, y</th>
<th>Total (n=23,349)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–5 (n=13,993)</td>
<td>5–10 (n=5,600)</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>104 (33)</td>
<td>90 (28)</td>
</tr>
<tr>
<td>Male</td>
<td>73 (32)</td>
<td>65 (28)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (37)</td>
<td>25 (30)</td>
</tr>
<tr>
<td>PCI</td>
<td>0 2 (11)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Male</td>
<td>2 (11)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Female</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Male</td>
<td>1 (13)</td>
<td>0 0</td>
</tr>
<tr>
<td>Female</td>
<td>0 1 (50)</td>
<td>0 1 (50)</td>
</tr>
</tbody>
</table>

Data are shown as number (percentage) of the patients. PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting.
would be necessary to further estimate the population at long-term risk from CAL sequelae, and such data are scarce. In a previous school survey of youngsters aged between 6 and 18 years, the prevalence was 103.9/100,000 in a cohort of 594 KD patients (mean follow-up, 12 years), the age-specific prevalence was highest among children <5 years (164.6/100,000), which is the most vulnerable age group for the occurrence of KD. The prevalence reflects the disease incidence and disease duration, and provides an adequate estimate of the disease burden. Those KD patients who did not have significant CAL might not continue their medical follow-up and tended to have a shorter disease duration. This subgroup’s low adherence to long-term treatment, and the relatively low incidence of KD between 1980 and 2000, might account for the lower prevalence rate observed in older age groups.

Among this national cohort of KD spanning 11 years, we also found that the average annual risk of coronary complications was significant, at 2.4%, and that the risk was greater among male than female patients (2.7% versus 2.0%). A recent study on a cohort of 38 KD patients revealed that symptoms and signs of myocardial ischemia were reported in 13% of the patients after a median follow-up of 8.5 years (range, 0.5–24.8 years). Myocardial infarction because of coronary arterial obstruction from CAL in KD patients tends to develop during the second week after disease onset, or later. The progression of coronary aneurysms to stenotic lesions is particularly prevalent in aneurysms with an internal diameter of at least 6 mm. An early study performed in the era before immunoglobulin therapy found that, among a cohort of 594 KD patients (mean follow-up, 12 years), AMI occurred in 11 (1.85%) (ie, at a rate of roughly 0.15% per year). According to the 20th national survey in Japan, risk of AMI was 0.02% during the 2-year follow-up. The present study found that risk of AMI in a national cohort spanning 11 years was only 0.08%. Considering the various findings together, the estimated risk of AMI in KD patients is ≈0.007% to 0.01% per year, in the current treatment era. The risk of AMI today is far lower than that reported in the early studies, which might be attributable to the early detection of index patients and early immune-modulation and antithrombotic therapy.

For patients in our study group who had coronary complications, PCI was performed in 1.44% of cases at a median age of 24.5 years; all patients in this subgroup were male. Although it is well-known that the incidence of KD is higher among males than females, the male/female ratio for long-term coronary risk and risk of PCI was even more marked for males. During the study period, the risk of PCI in the non-KD general population aged <40 years was 0.0019% (unpublished data), which is considerably lower than that in KD patients (0.078%). In the adult population <60 years, men exhibit a higher incidence of coronary heart disease compared with women, and higher coronary heart disease mortality rates at every age. The sex difference in risk has been attributed to hormone-related glucose and lipid metabolism; such sex-related risk might also contribute to the progression of CAL in male KD patients. In a previous multicenter study, PCI was performed in 57 KD patients at a median age of 12.1 years, and the male/female ratio (4.2) was also high. The overall success rate was ≈74% and was inversely related to the interval between disease onset and the time point of PCI. No procedure-related mortality was reported in either that study or our own.

In our KD patient group, CABG was performed in 0.043% of cases and in 0.80% of patients with coronary complications, again with a male predominance (male/female ratio, 4.0). During the study period, the risk of CABG in the non-KD general population <40 years was only 0.0002% (Dr Wu, unpublished data, 2000–2010), which was substantially lower than the risk of CABG in KD patients (0.043%). Japan’s national survey in 2002 reported that CABG was performed in roughly 30 patients every year, more often in males than females (male/female ratio, 3.36). The number of new KD patients was ≈6000 to 8000 annually; thus, the Japanese researchers deduced that the risk of CABG was roughly 0.5%. However, they did not address the question of long-term risk based on prevalence data.

In the present study, only 10 patients received CABG during the 11 years of the study period. Compared with the epidemiological data from Japan, the number of new patients in Taiwan was ≈10%, whereas the number of patients receiving CABG was 3% of that in Japan. The mortality was relatively high (25%) among our patients. A recent separate survey of 148 KD patients who received coronary intervention (67 patients with PCI and 81 with CABG) found that CABG mortality was only 5.0%. These 2 sets of findings suggested that KD patients in our study group might have been referred for CABG at relatively advanced disease stages, but this hypothesis needs to be confirmed by future research.

The current study was subject to certain limitations. First, it was based on the NHI database and mortality data could only be defined as mortality at discharge. Any possible association between the intervention procedure and patient death could not be directly validated. Second, our study design and data type did not allow for the severity of CAL to be assessed; thus, we could not examine the effect of disease severity of CAL on subsequent coronary risk. Future studies in which patient data could be matched with medical record reviews to elucidate the relationship between the severity of CAL and subsequent risk would be helpful. These studies might be limited to selected geographical regions of Taiwan for the sake of feasibility.

In conclusion, this nationwide database study estimated the overall prevalence of KD in the general population <40 years and the risk of myocardial ischemia or infarction in KD patients. The estimated KD prevalence was 34.9/100,000, and the estimated annual coronary risk in KD patients was 2.4%. In all age groups, male patients were at higher risk of coronary complications, and males received more coronary interventions than did females. Risk stratification to facilitate timely coronary intervention and risk modification for KD patients is mandatory.

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Disclosures

None.

References


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