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Original Article

Epidemiologic features of Kawasaki disease in acute stages in Taiwan, 1997−2010: Effect of different case definitions in claims data analysis

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Abstract

Background: Kawasaki disease is the leading cause of pediatric acquired cardiac disease in many industrialized countries. The aim of this study was to estimate the incidence of Kawasaki disease in acute stages in Taiwan, by linking the diagnosis code to medication and comparing the differences in epidemiological features with those of previous reports that used the diagnosis code alone.

Methods: We searched the National Health Insurance Research Database from 1997 to 2010. For the International Classification of Diseases, Ninth Revision (ICD-9) set, all inpatients with a main diagnosis of Kawasaki disease (ICD-9, 446.1) were retrieved. For the ICD-9 + intravenous immunoglobulin (IVIG) set, Kawasaki disease in acute stages was defined as the disease stages requiring IVIG. The epidemiologic features were calculated and compared by both methods.

Results: The incidence rates for children under 5 years ranged from 21.5 to 68.5 per 100,000 person-years (average 49.1) for the ICD-9 + IVIG set and from 48.5 to 82.8 per 100,000 person-years (average 74.9) for the ICD-9 set. Significant discrepancy in peak season estimation occurred in summer. The 5-year recurrence rate was 1.1% for the ICD-9 + IVIG set and 4.5% for the ICD-9 set. The coronary complication rates were around 7.24% (ICD-9 + IVIG) and 6.48% (ICD-9).

Conclusion: Discrepancies occurred when different case definitions were used in claims data analysis. Previous reports might have overestimated the incidence, recurrence rate, and complication rate in older children. The new method might slightly underestimate them. The true incidence might lie in between.

Keywords: claims data; epidemiology; Kawasaki disease; seasonal variations

1. Introduction

Kawasaki disease is an acute, self-limited, systemic vasculitis.[1] It is now the leading cause of acquired cardiac disease in children in many industrialized countries.[2−10] It may induce coronary artery abnormalities ranging from transient ectasia and small aneurysms to giant aneurysms.[11−13] Prompt diagnosis and timely administration of intravenous immunoglobulin (IVIG) are crucial to prevent coronary complications.[1,14−18] Thus, estimating the incidence of Kawasaki disease in acute stages is important for understanding the disease burden and public health policy making.

Incidences of Kawasaki disease in different countries were reported previously.[3−10,13,19−21] Most of the data were derived from either claims data analysis or hospital surveys. Few countries have a Kawasaki disease registry.[4] The incidence of Kawasaki disease in Taiwan has also been reported previously.

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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Both hospital surveys and claims data from the National Health Insurance (NHI) have been used.[6,19,20] However, there are some discrepancies in the data derived from these two resources (Table 1).[6,19,20] The hospital survey is regarded as noncomprehensive and subject to double counting when patients are transferred between hospitals. As the NHI has been available in Taiwan since 1996 and covers more than 98% of the population,[22,23] epidemiologic data retrieved from its database are regarded as more reliable and comprehensive. However, previous reports using claims data from the NHI focused on admission with a main diagnosis code of Kawasaki disease. Whether the reason for admission was the acute stages of this disease or not was not well defined.[6,19] This might somewhat overestimate the disease incidence.

As IVIG therapy is covered by the NHI when an acute episode of Kawasaki disease is diagnosed, including incomplete Kawasaki disease, most patients in Taiwan receive IVIG in the initial stage of illness. Therefore, Kawasaki disease in acute stages could possibly be defined by analyzing the use of IVIG. The aim of this study was to estimate the incidence of Kawasaki disease in acute stages in Taiwan, by linking the diagnosis code to medication and comparing the differences in the epidemiological features with those of previous reports that used the diagnosis code alone.

2. Methods

This was a retrospective cohort study. Although the NHI of Taiwan was initiated in 1995, the database for that year was incomplete. We, therefore, searched the National Health Insurance Research Database (NHIRD) of Taiwan to collect patients' medical records from 1997 to 2010. Files of inpatient expenditure by admission (DD1997–DD2010 files) and details of inpatient orders (DO1997–DO2010 files) were the main resources for data analysis.

For the International Classification of Diseases, Ninth Revision (ICD-9) set, medical records of all inpatients whose first or second diagnosis was Kawasaki disease (ICD-9, 446.1) were retrieved. On the other hand, for the ICD-9 + IVIG set, in addition to the first or second diagnosis fulfilling the criteria for Kawasaki disease (ICD-9, 446.1), we further cross-linked the details of inpatient orders to see if patients were treated with IVIG. Patients were regarded as having received IVIG therapy if their inpatient orders included medication whose anatomical therapeutic classification code was J06BA02. Coronary aneurysm was identified by any discharge diagnosis, including ICD-9 414.11. Recurrence was defined as readmission of patients with a main diagnosis of Kawasaki disease in the ICD-9 set, and readmission of patients with a main diagnosis of Kawasaki disease and receipt of immunoglobulin in the ICD-9 + IVIG set. If two admissions were within 30 days, they were regarded as being in the same acute stage. If two admissions of the same patient were separated by more than 30 days, they were regarded as two episodes of Kawasaki disease in acute stages.

Table 1
Comparison of incidence, recurrence, and coronary artery complication rates among previous series and this study.

	Incidence rate [a]	Recurrence rate (%)	Coronary artery complication rate (%)
Lue et al[20]	55	—	25.8
Chang et al[19]	66	1.3	7.3
Huang et al[6]	69	1.5	7.2
This study	49	1.1	7.2

[a] Incidence rate unit: 100,000 children aged under 5 years per year.

Patients' sex, age, and date of admission were retrieved. The annual incidence, monthly distribution of patients, sex distribution, recurrence rate, and complication rate were calculated. The population statistics were obtained from the website of the Ministry of the Interior, Taiwan.

According to the NHIRD, data that could be used to identify patients or care providers, including medical institutions and physicians, are scrambled before being sent to the National Health Research Institutes for database construction and are further scrambled before being released to individual researchers (http://w3.nhri.org.tw/nhird//en/Data_Protection.html). A written agreement declaring there would be no attempt to obtain information that could potentially violate the privacy of patients or care providers was signed before the beginning of data retrieval. This analysis was conducted for research purposes only. There is no potential conflict of interest. The computer-processed personal data protection law and related regulations of the Bureau of NHI and the National Health Research Institutes of Taiwan were strictly followed. The protocol was reviewed and approved by the National Health Research Institutes prior to data release. The study protocol has also been approved by the institutional review board of Taichung Veterans General Hospital.

SAS 9.1 for Windows (SAS Institute, Inc., Cary, NC, USA) was used for data retrieval and data analysis. Chi-square tests were applied for categorical data comparisons. The Poisson regression model was used for comparing incidences. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Annual incidences per 100,000 children aged under 5 years and sex distributions

The demographic data are summarized in Table 2. The annual incidence rates per 100,000 children <5 years old are shown in Table 3. When we calculated the number of patients with the ICD-9 code alone, the incidences ranged from 48.5 to 82.8 per 100,000 children <5 years of age. The average incidence from 1997 to 2010 was 74.9 per 100,000 children under 5 years of age. When we calculated the number of patients treated with IVIG, the incidences ranged from 21.5 to 68.5 per 100,000 children. The average incidence from 1997 to 2010 was 49.1 per 100,000 children under 5 years of age. There were significant discrepancies between these two sets of data. The difference was more significant in 2003, when a severe acute respiratory syndrome (SARS) outbreak occurred in Taiwan. The incidences declined significantly during the

Table 2
Demographic data for study cohort.

	ICD-9	ICD-9 + IVIG
Patient numbers	13179	8270
Sex [a]		
Male	8223 (62.5%)	5142 (62.3%)
Female	4933 (37.5%)	3116 (37.7%)
Age group **		
0–1 y	4670 (35.4%)	3210 (38.8%)
1–2 y	3551 (26.9%)	2317 (28.0%)
2–3 y	1867 (14.2%)	1240 (15.0%)
3–4 y	1034 (7.8%)	606 (7.3%)
4–5 y	706 (5.4%)	389 (4.7%)
Coronary aneurysms	894 (6.8%)	599 (7.2%)

** $p < 0.001$.
ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.
[a] Data were missing for 23 cases in the ICD-9 group and 12 in the ICD-9 + IVIG group.

SARS outbreak in the spring of 2003, when we calculated the number of patients by using ICD-9 + IVIG. There were no major differences in sex distribution between these two sets of data. The male-to-female ratio was around 1.7.

3.2. Monthly distribution of patients

Patient distributions by months are summarized in Table 4. In calculation of the distribution using the ICD-9 alone, the peak months were May–July. However, in calculation of the distribution using both ICD-9 and IVIG, the peak months were April–June. The discrepancy between the two methods was greater during the summer vacation period (July and August). If only children older than 5 years of age were analyzed, the peak months were February, July, and August in the ICD-9 set. These 3 months are winter and summer vacations in Taiwan.

Table 3
Annual incidence of Kawasaki disease in Taiwan (per 100,000 children <5 years of age) using the ICD-9 data alone or the ICD-9 + IVIG data.

Year	Population under 5 y	ICD-9 [a]		ICD-9 + IVIG [a]	
		Cases	Incidence	Cases	Incidence
1997	1,599,094	775	48.46	344	21.51
1998	1,545,889	1019	65.92	583	37.71
1999	1,507,221	939	62.30	659	43.72
2000	1,489,242	949	63.72	637	42.77
2001	1,426,759	988	69.25	726	50.88
2002	1,350,829	879	65.07	381	28.20
2003	1,309,903	754	57.56	307	23.44
2004	1,243,939	815	65.52	438	35.21
2005	1,144,355	824	72.01	496	43.34
2006	1,092,942	821	75.12	683	62.49
2007	1,052,585	742	70.49	598	56.81
2008	1,026,206	808	78.74	662	64.51
2009	1,002,160	707	70.55	581	57.97
2010	964,093	798	82.77	660	68.46

ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.
[a] Statistically significant difference between two methods of estimating incidence by Poisson regression model.

Table 4
Monthly distribution of Kawasaki disease patients (all ages) using the ICD-9 data alone or the ICD-9 + IVIG data.*

Month	Patient number	
	ICD-9	ICD-9 + IVIG
January	766	485
February	818	539
March	1036	691
April	1081	745
May	1186	782
June	1186	811
July	1123	677
August	1046	679
September	1015	661
October	969	632
November	841	565
December	761	495

* $p = 0.41$ for February, July, and August.
ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.

However, in the ICD0 + IVIG set, these two peaks were not seen (Table 5).

3.3. Recurrence rate

When ICD-9 alone was used as the indicator of Kawasaki disease, about 5.52% of patients had more than one episode of this disease. However, when both ICD-9 and IVIG were used as indicators, only 1.16% of patients had more than one episode. The distribution of recurrent episodes is summarized in Table 6. The cumulative recurrence rates estimated by two definitions are depicted in Fig. 1. The 5-year recurrence rate calculated by the Kaplan–Meier method was 1.1% for the ICD-9 + IVIG set and 4.5% for the ICD-9 set. The median recurrence time was about 401 days for the ICD-9 + IVIG set and 313 days for the ICD-9 set.

Table 5
Monthly distribution of Kawasaki disease patients using the ICD-9 data alone or the ICD-9 + IVIG data for children older than 5 years of age.*

Month	Patient number	
	ICD-9	ICD-9 + IVIG
January	97	38
February	142	61
March	113	51
April	111	43
May	134	59
June	99	38
July	159	43
August	140	35
September	102	47
October	95	33
November	85	29
December	74	31

* $p = 0.040$ for February, July, and August.
ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.

Table 6
Number of recurrent episodes per patient number using the ICD-9 data alone or the ICD-9 + IVIG data.

ICD-9			ICD-9 + IVIG		
Episode	Patient number	%	Episode	Patient number	%
1	12,452	94.48	1	8174	98.84
2	476	3.61	2	87	1.05
3	150	1.14	3	4	0.05
4	53	0.4	4	1	0.01
5	24	0.18	5	1	0.01
6	12	0.09	6	1	0.01
7	5	0.04	7	1	0.01
8	4	0.03	8	1	0.01
9	2	0.02	9	0	0
10	1	0.01	10	0	0

ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.

3.4. Complication rate (coronary aneurysm) stratified by age

The complication (coronary aneurysm) rates calculated by both methods in different age groups are summarized in Fig. 2. The average complication rate was 6.78% when calculated by using ICD-9 alone. However, the average rate was 7.24% when calculated using the ICD-9 + IVIG. As shown in Fig. 2, the complication rate was as high as 30% in older children using the ICD-9 alone. However, there were almost no patients older than 9 years with an aneurysm when ICD-9 + IVIG were used. This may reflect that patients who were admitted for a survey later in life were regarded as incidence cases if we used ICD-9 alone to identify Kawasaki disease in acute stages.

4. Discussion

In this study, we used a specific therapy, IVIG, as the indicator of Kawasaki disease in acute stages and tried to reanalyze the epidemiologic features of this disease in Taiwan. The annual incidences of Kawasaki disease, which ranged from 21.5 to 68.5 per 100,000 person-years for children under 5 years, were lower than previously reported data obtained using the NHIRD.[6,19] Previous reports using only ICD-9 coding to analyze claims data were subject to overestimation of the incidence of acute stages because physicians might code Kawasaki disease as the main diagnosis when patients had not been admitted for acute stages, for example, in case of admission for angiography, computed tomography, or coronary intervention. Moreover, because Kawasaki disease is regarded as a life-long catastrophic disease under the NHI scheme of Taiwan, physicians have to code Kawasaki disease as the main diagnosis for their patients to eliminate copayments when those patients are admitted due to other diseases such as enterocolitis or pneumonia.

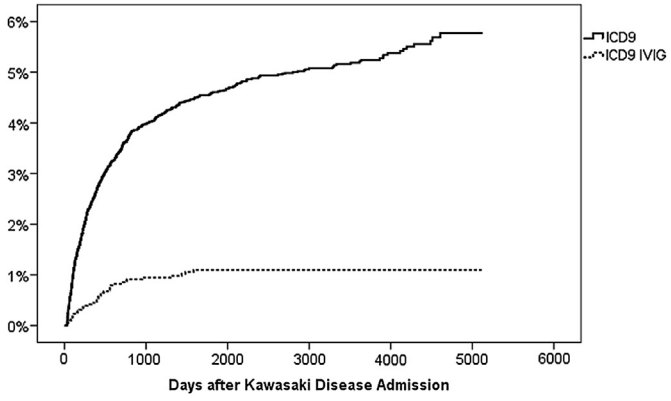

Fig. 1. Cumulative recurrence rates of Kawasaki disease calculated by different case definitions. ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.

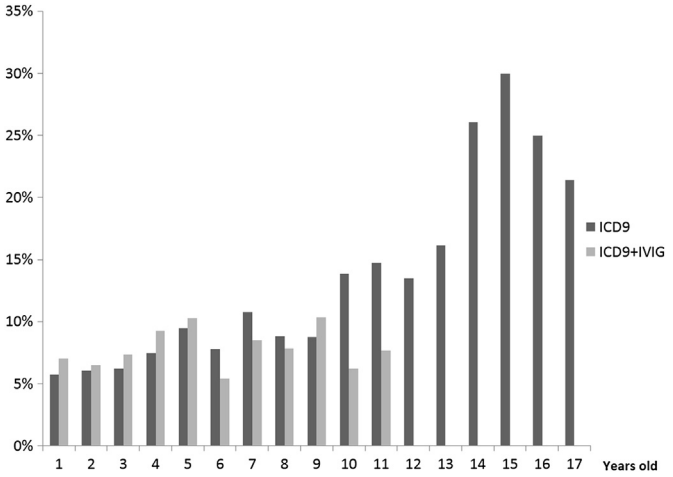

Fig. 2. Proportions of patients with coronary aneurysm in different age groups, using the ICD-9 data alone or the ICD-9 + IVIG data. ICD-9 = International Classification of Diseases, Ninth Revision; IVIG = intravenous immunoglobulin.

The average incidence with IVIG therapy was 49.1 per 100,000 person-years for children under 5 years, and it was slightly higher than the incidence in Hong Kong (39) and similar to that in Beijing (40.9–55.1).[2,8] From a geographic perspective, Japan and Korea have the highest and second highest incidences in the world, 239.6 and 105.0, respectively.[9,10,13] Taiwan is geographically near to Hong Kong. Moreover, most people in Taiwan are descendants of Chinese people. Therefore, the incidence in Taiwan should be similar to that in China. Hence, from both a geographic and a genetic viewpoint, the results of our study are feasible. Some might argue that this method might underestimate the incidence of Kawasaki disease because there must be some patients who were diagnosed late and not given IVIG. However, Kawasaki disease is regarded as a catastrophic disease by the Bureau of NHI, and the cost of IVIG is covered. Pediatricians in Taiwan are familiar with Kawasaki disease. Therefore, we do not think that many patients were misdiagnosed, as we show in Table 3. Furthermore, if a patient was afebrile at the time of diagnosis, there was no indication for admission.

The seasonal clustering of Kawasaki disease in acute stages in our study was different from that of previous reports when IVIG therapy was used as the indicator. Two previous reports claimed that Taiwan had the most patients in summer.[6,19] This

may reflect that certain cases were repeatedly counted when they were not admitted for Kawasaki disease in acute stages. Our results revealed that the peak season in Taiwan was late spring to early summer (April−June). Spring is warm and humid in Taiwan, which facilitates the transmission of airborne infectious diseases. Moreover, our study showed that the incidence declined when the SARS outbreak occurred in 2003. Huang et al's[6] study failed to take this phenomenon into account. At the time of SARS outbreak, people, including young children and infants, were confined to their houses and came in contact with others less often. As a result, transmission of viral illness among young children might have been reduced. This provides some support to one hypothesis about the pathogenesis of Kawasaki disease, which states that Kawasaki disease is an immune reaction caused by some kinds of infectious agents.[1,15,24] Our results using IVIG as the indicator are similar to those found in reports from Hong Kong and Beijing and somewhat different from those found in reports from Japan and Korea.[2,8−10] We believe that our results are more reasonable from both a geographic and a genetic perspective, as we mentioned above. When we counted only children older than 5 years of age, we found that the number of patients was highest in February, July, and August. These 3 months are winter and summer vacations in Taiwan. This finding might suggest that some children with a past history of Kawasaki disease were admitted for survey during their vacations. This phenomenon might have influenced the results of previous reports (Tables 4 and 5).[6,19]

When we used ICD-9 alone as the indicator, the recurrence rate was 5.52%. It was higher than that of a previous report by Huang et al[6] (1.5%). We believe that the discrepancy is caused by the shorter study period (2003−2006) of their report. Therefore, a certain number of patients were censored. However, the recurrence rate was 1.16% when we used IVIG as the indicator. In comparison with Japan (3%), the recurrence rate was significantly lower in Taiwan.[10] The lower incidence of Kawasaki disease in Taiwan might contribute to the lower recurrence rate. These discrepancies also reflect a possible fallacy in the methodology of previous studies. As physicians code Kawasaki disease as the main diagnosis to receive reimbursement for catastrophic disease from the Bureau of NHI and avoid peer review, the recurrence rate should have been overestimated in previous reports.[6,19] Table 6 shows that 251 patients (1.9%) had more than two episodes of Kawasaki disease in the ICD-9 set. Kawasaki disease usually recurs only once.[10] On the contrary, if we use IVIG as the indicator, only nine patients (0.1%) had more than two episodes. We believe that the patients who had more than five episodes were outliers. However, we do not think that the estimation of recurrence rate would not be influenced significantly using IVIG as an indicator.

Huang et al[6] reported that the development of coronary aneurysms was associated with older age. When we used IVIG as the indicator of acute stages, this association disappeared. This reflected another possible fallacy in the methodology of previous studies. Children with a past history of Kawasaki disease and coronary aneurysms could be included in a survey when they reached school age, but that does not mean that they should be regarded as acute cases. Although older age has been reported to be a risk factor for coronary aneurysm in the United States,[14] we do not believe that this association exists in Taiwan. Some might argue that the diagnosis of older children might be delayed and hence the timing of IVIG administration might be missed. However, it is hard to believe that all the patients older than 9 years were misdiagnosed and not given IVIG. Previous reports from Taiwan noted that older age, being a risk factor for complications, might actually reflect some patients who were readmitted for survey, and the disease in not for acute stages.[6,19] The coronary aneurysm rates could be underestimated because the aneurysms could develop later, after discharge from hospital. However, in order to compare with previous reports,[6,19] we adopted only the diagnosis codes at admission.

This study used data from the NHIRD, which includes almost the entire children population of Taiwan.[22,23] We believe that it offers an accurate evaluation of the incidence and epidemiological features of Kawasaki disease in the study period. However, this study has some limitations. First, patients' ID numbers were scrambled before being released to individual researchers, so it is almost impossible to test the validity of the results at the individual level. Second, the severity of aneurysm could not be identified by the diagnosis codes alone. Therefore, we do not know whether the aneurysm was transient or persistent after the acute stages. Third, laboratory test results were not included in the claims data. As a result, we could not analyze the association between laboratory data and disease severity.

In conclusion, using different case definitions in claims data analysis led to discrepancies. Previous reports might overestimate the incidence, recurrence rate, and complication rate in older children. The new method might slightly underestimate these parameters. The true incidence might lie in between these two methods.

Acknowledgments

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