Epidemiology, Treatments, and Cardiac Complications in Patients with Kawasaki Disease: The Nationwide Survey in Japan, 2017-2018

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Objective To report the epidemiologic characteristics, treatments, and cardiac complications of Kawasaki disease, using data from the nationwide survey in Japan.

Study design The nationwide Kawasaki disease survey in Japan has been conducted biennially since 1970. The most recent survey was completed in 2019, obtaining information for patients who developed Kawasaki disease during 2017-2018. Survey respondents were hospitals specializing in pediatrics and those with ≥100 beds and a pediatric department throughout Japan, where patients with Kawasaki disease were eventually hospitalized.

Results The survey identified 32 528 patients with Kawasaki disease, which consisted of 15 164 (46.6%) in 2017 and 17 364 (53.4%) in 2018. The highest annual incidence rate was recorded in 2018 (359 per 100 000 children aged 0-4 years). After 1982, patients with ≤4 principal Kawasaki disease signs gradually increased, resulting in 6847 (21.1%) patients diagnosed during 2017-2018. Among the 30 784 patients receiving initial intravenous immunoglobulin administration, 6061 (19.7%) did not respond. Within 30 days of Kawasaki disease onset, 9.0% of patients were diagnosed with cardiac complications, and 2.6% of patients developed cardiac sequelae after the acute illness.

Conclusions The annual number of patients developing Kawasaki disease in Japan increased from 1970 through 2018, whereas the proportion of patients with Kawasaki disease with cardiac complications decreased in the most recent 2 decades. Early diagnosis of Kawasaki disease as well as advances in initial treatments could explain these findings. *(J Pediatr 2020;225:23-9)*.

Kawasaki disease is an acute systemic vasculitis that occurs in young children. Some patients with Kawasaki disease can develop coronary artery abnormalities (CAAs), such as coronary aneurysms, resulting in cardiac sequelae after acute illness. Kawasaki disease is now the most common cause of acquired pediatric heart disease in developed countries.[1-3] Since the first report by Dr Tomisaku Kawasaki in 1967, Kawasaki disease has been reported in >60 countries and areas worldwide, as well as in children of all races and ethnicities, but the incidence remains highest in Japan.[4-11] The number of patients with Kawasaki disease has recently increased worldwide; nevertheless, the etiology of Kawasaki disease remain largely unidentified.

A nationwide Kawasaki disease survey in Japan has been conducted biennially since 1970 to monitor patients with Kawasaki disease who occurred throughout Japan. The survey covers almost all medical facilities across the country where patients with Kawasaki disease are eventually hospitalized, and thus can be considered a census survey of patients with Kawasaki disease from Japanese general population. The latest survey was completed in 2019 and updated previous epidemiologic data describing Kawasaki disease in Japan. Highlighting the data from the most recent survey, the present study aimed to summarize the recent epidemiologic and clinical trends in Kawasaki disease in Japan, partially compared with those observed in previous years.

Methods

The 25th Japanese nationwide Kawasaki disease survey was conducted in 2019. This was a cross-sectional survey that aimed to obtain information for patients who developed Kawasaki disease across Japan from January 1, 2017, through December 31, 2018. Survey respondents represented 2 types of medical facilities from throughout Japan—hospitals specializing in pediatrics and hospitals with ≥100 beds and a pediatric department. These facilities covered most hospitals in Japan where patients with Kawasaki disease are eventually hospitalized and treated by pediatricians with Kawasaki disease expertise. To accurately select the facilities, we used the 2017-2018 Listing of Hospitals compiled by the Committee on Studies of Health Policies, Ministry of Health, Labour and Welfare, Japan, which resulted in 1804 eligible facilities. Questionnaires were sent by mail or e-mail to representative pediatricians at the selected facilities, and each recorded all patients with Kawasaki disease who visited their facilities during 2017-2018. The Japanese guidelines were used to diagnose and treat patients with Kawasaki disease.[12-14] The survey outline has not been revised

CAA	Coronary artery abnormality
IVIG	Intravenous immunoglobulin

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since the first survey was conducted in 1970. The survey was conducted every 2 years; the 24th survey data were previously documented.[11]

Case Definition of Kawasaki Disease

The 6 principal signs of Kawasaki disease are (1) fever persisting ≥5 days (or previous defervescence in response to treatment), (2) bilateral conjunctival injection, (3) oral mucosal changes, (4) polymorphous skin rash, (5) peripheral extremity changes, and (6) cervical lymphadenopathy. Patients with 5 or 6 principal signs were defined as having complete Kawasaki disease.

The case definition of patients with Kawasaki disease with ≤4 principal signs differs between Japan and other countries.[3,12] Based on the Japanese diagnostic criteria, patients with ≤4 principal signs comprise "atypical definite Kawasaki disease" and "incomplete Kawasaki disease" cases.[12] Patients with atypical definite Kawasaki disease are defined as having 4 of 6 principal signs in combination with CAAs, and other cases as having "incomplete Kawasaki disease."

Measurements

The survey obtained demographic characteristics, treatments, and cardiac complications for patients with Kawasaki disease. The demographic characteristics comprised age, sex, recurrent status (prior history of Kawasaki disease), sibling and parent history of Kawasaki disease, the number of principal Kawasaki disease signs, and day of illness at admission. The first day of illness was defined as the first day presenting signs related to Kawasaki disease (ie, the day of Kawasaki disease onset).

Treatment information consisted of initial intravenous immunoglobulin (IVIG) with the day of illness at administration as well as subsequent nonresponsiveness to the administration. IVIG nonresponders were defined as patients who developed recurrent or persistent fever (≥37.5°C) ≥24 hours after the end of their initial IVIG administration. Nonresponders could receive additional specific treatments as secondary or later treatments after the initial IVIG administration, which were also recorded in the survey. Additional specific treatments were additional IVIG, corticosteroids, infliximab, immunosuppressive drugs, and/or plasma exchange.

The survey also obtained information on cardiac complications resulting from Kawasaki disease, which were evaluated by 2-dimensional echocardiography, including CAAs and valvular lesions. CAA subtypes were typically based on the definition from the Japanese Ministry of Health.[14,15] Coronary artery dilatation was defined as a maximum absolute internal lumen diameter of ≥3 mm with any finding of local dilatation in children aged <5 years or a diameter of ≥4 mm in children aged ≥5 years. Coronary artery aneurysm was defined as lumen size of 4-8 mm or ≥1.5 times greater than that of an adjacent segment, and giant coronary artery aneurysm as lumen size ≥8 mm. Multiple types of CAAs could be detected in the same patient (eg, coronary artery aneurysms with dilatations). Cardiac complications were recorded as being detected during acute illness (<30 days from Kawasaki disease onset) or postacute illness periods (≥30 days from Kawasaki disease onset), which were defined as cardiac sequelae.

Statistical Analyses

We analyzed the survey data using descriptive epidemiologic methods simply to provide real-world evidence. Categorical variables are presented as the percentage of patients, and medians and IQRs are also presented for numerical variables. The incidence rates of Kawasaki disease were calculated by referring to the population data in the vital statistics data for Japan. The age-specific incidence rate was calculated using the recent survey data for patients who developed Kawasaki disease from 2017 through 2018. Incidence rates were not adjusted for the response rates of the surveys. Annual trends in Kawasaki disease incidence corresponding with the total number of patients with Kawasaki disease, including the percentage of patients with ≤4 principal Kawasaki disease signs, were described using the data from the 1st to 25th surveys, which provided information for patients who developed Kawasaki disease from 1970 through 2018. In addition, we described annual trends in the proportion of cardiac complications detected during both acute and postacute illness in the last 2 decades. This study was approved by the Jichi Medical University Clinical Research Ethics Committee (Receipt ID: 18-070).

Results

Of the 1804 eligible facilities, 1357 (75.2%) responded to the survey. A total of 32 528 patients were identified, including 15 164 (46.6%) and 17 364 (53.4%) patients who developed Kawasaki disease in 2017 and 2018, respectively (**Table I**; available at www.jpeds.com). The median age at disease onset was 27 months, and 18 599 (57.2%) patients were males. Among all patients, 1478 (4.6%) had recurrent Kawasaki disease. Patients who had a sibling and parental histories of Kawasaki disease numbered 696 (2.2%) and 419 (1.3%), respectively. Patients were admitted at a median of 4 days from disease onset, which remained unchanged for >2 decades (data not shown). The seasonality of Kawasaki disease in the most recent survey slightly differed from those in previous surveys (**Figure 1**; available at www.jpeds.com).

The highest annual number of patients with Kawasaki disease for all survey years was recorded in 2018, corresponding with the incidence rate of Kawasaki disease, which was also the highest in 2018 at 359 (per 100 000 children aged 0-4 years per year) (**Figure 2**). In addition, the percentage of patients with ≤4 principal Kawasaki disease signs increased over the survey years from a minimum of 7.0% in 1982 to >20.0% of all the patients after 2007, indicating that the proportion of patients with complete Kawasaki disease conversely decreased over the survey years after 1982. Based on the Japanese diagnostic criteria, patients with atypical definite Kawasaki disease was 1.7% of all the patients during 2017-2018.

The age-specific incidence rates during 2017-2018 were highest in children aged 9-11 months in both boys and girls (572 and 398 per 100 000 children per year, respectively), after which the rate decreased with age (**Figure 3**; available at www.jpeds.com).

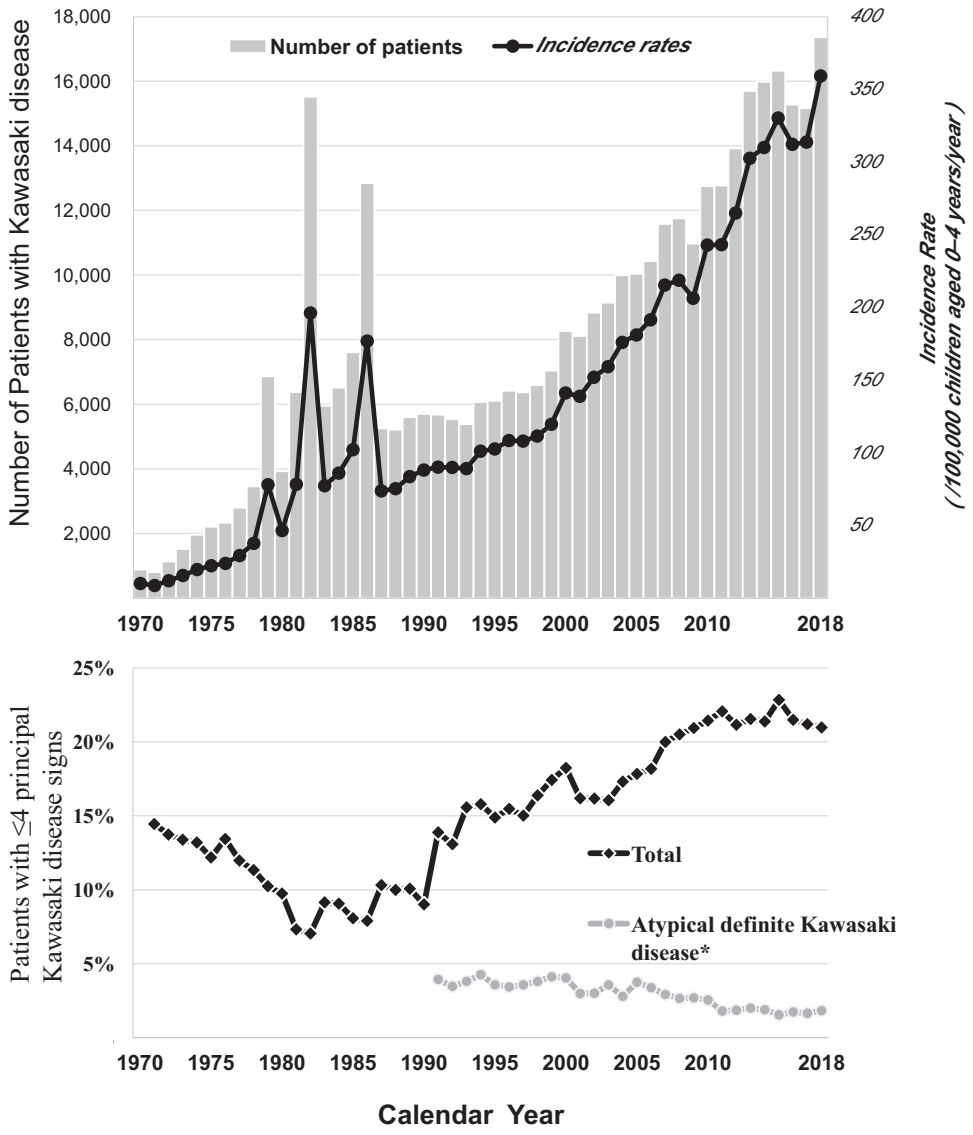

Figure 2. Annual number of patients, incidence rates, and percentage of patients with ≤4 principal signs of Kawasaki disease: the nationwide survey in Japan, 1970-2018. *Atypical definite Kawasaki disease is defined as patients with 4 of 6 principal signs in combination with CAAs, based on the Japanese diagnostic criteria.

A total of 30 784 (94.6%) patients received initial IVIG administration at a median of 5 days from disease onset during 2017-2018 (**Table II**). The median days also remained unchanged for >2 decades. Among the 30 784 patients receiving initial IVIG administration, 6061 (19.7%) patients did not respond to the initial IVIG treatment (nonresponders). Patients who received corticosteroid combination use with initial IVIG increased from 3.2% (n = 371) in 2011 to 13.3% (n = 2184) in 2018 (**Figure 4**; available at www.jpeds.com). Additional IVIG, corticosteroids, infliximab, immunosuppressive drugs, and/or plasma exchange treatments were given as secondary or later treatments subsequent to initial IVIG treatment for 6663 (21.6%), 1933 (6.3%), 790 (2.6%), 449 (1.5%), and/or 162 (0.5%) patients, respectively.

During 2017-2018, cardiac complications were detected in 2895 of 32 236 patients with Kawasaki disease (9.0%) without missing data during acute illness (<30 days from disease onset), and cardiac sequelae were detected in 843 of 31 875 (2.6%) during postacute illness periods (≥30 days from onset) (**Table III**). In acute illness, 2464 (85.1%) and 503 (17.4%) patients were detected CAAs and valvular lesions, respectively, whereas in postacute illness, 689 (81.7%) and 164 (19.4%) were diagnosed as having cardiac sequelae, respectively. In both illness periods, a greater proportion of male patients had CAAs, whereas a greater proportion of females had valvular lesions. Among 2885 patients with cardiac complications detected in acute illness periods, 1298 (45.0%) patients had complications identified at admission (**Table IV**; available at www.jpeds.com).

Decreasing trends were found in the percentage of cardiac complications in the most recent 2 decades (1999-2018) in

Table II. Treatments for patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018 (n = 32 528)

Treatments	Total (n = 32 528)	Year	
		2017 (n = 15 164)	2018 (n = 17 364)
Initial IVIG administration			
None	1744 (5.4)	853 (5.6)	891 (5.1)
IVIG only	26 708 (82.1)	12 419 (81.9)	14 289 (82.3)
IVIG combined with corticosteroids	4076 (12.5)	1892 (12.5)	2184 (12.6)
Days of illness at initial IVIG administration*	5 (4-6)	5 (4-6)	5 (4-6)
Initial IVIG nonresponders*	6061 (19.7)	2838 (19.8)	3223 (19.6)
IVIG only†	5066 (19.0)	2367 (19.1)	2699 (18.9)
IVIG combined with corticosteroids†	995 (24.4)	471 (24.9)	524 (24.0)
Additional specific treatments after initial IVIG‡	(n = 30 784)	(n = 14 311)	(n = 16 473)
None	23 582 (76.6)	10 951 (76.5)	12 631 (76.7)
Additional IVIG	6663 (21.6)	3092 (21.6)	3571 (21.7)
Corticosteroids	1933 (6.3)	904 (6.3)	1029 (6.2)
Infliximab	790 (2.6)	331 (2.3)	459 (2.8)
Immunosuppressive drugs§	449 (1.5)	185 (1.3)	264 (1.6)
Plasma exchange	162 (0.5)	80 (0.6)	82 (0.5)

Values are number (%) or median (IQR).
*Excluding patients who did not receive initial IVIG administration.
†Percentages were calculated for each treatment type.
‡Some patients received multiple specific treatments; therefore, the number totals do not much, and percentages do not total 100%.
§The survey data is not available on the specific type of immunosuppressive drugs.

both acute and postacute illness, although the percentage slightly increased after 2015 (Figure 5). During 2015-2018, the percentage of IVIG nonresponders corresponded with the trend toward increased numbers of patients with cardiac complications in both illness periods.

Discussion

The survey data highlight that the annual number of patients who developed Kawasaki disease in Japan has increased consistently since 1970, with the highest number in 2018. Epidemics of Kawasaki disease occurred 3 times: in 1979, 1982, and 1986, but no such epidemics occurred after 1987. In contrast, the annual percentage of cardiac complications in patients with Kawasaki disease decreased in the most recent 2 decades. In acute and postacute illness periods, cardiac complications/sequelae decreased from 18.8% and 6.2% in 1999 to minimums of 7.9% and 2.2% in 2015, respectively. During 2015-2018, these proportions increased slightly, along with increased numbers of initial IVIG nonresponders, which should be continuously monitored in the future.

Despite the recent declining birthrates in Japan, the number of patients with Kawasaki disease continues to increase. Several possible reasons could explain this finding. First, pediatricians across Japan may now more appropriately recognize and diagnose patients suspected of having Kawasaki disease. With advances in echocardiography as well as the improved physician of diagnostic skills, cardiac complications, especially CAAs, may have been detected in the early days of illness from Kawasaki disease onset. Our results showed that approximately one-half of the patients (45%) were identified as having cardiac complications at admission. Previous studies worldwide reported that early detection of CAAs helps to distinguish Kawasaki disease from other febrile illnesses, indicating that echocardiography should be promptly performed when Kawasaki disease is first suspected.[16-22] Early Kawasaki disease diagnosis, before the maximum number of principal Kawasaki disease signs appear, could have contributed to the annual

Table III. Cardiac complications in patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018

Cardiac complications	Acute illness period* (<30 d from Kawasaki disease onset)			Postacute illness period (cardiac sequelae)* (≥30 d from Kawasaki disease onset)		
	Total (n = 32 236)	Male (n = 18 414)	Female (n = 13 822)	Total (n = 31 875)	Male (n = 18 200)	Female (n = 13 675)
Total†	2895 (100)	1845 (100)	1050 (100)	843 (100)	547 (100)	296 (100)
CAA‡	2464 (85.1)	1618 (87.7)	846 (80.6)	689 (81.7)	472 (86.3)	217 (73.3)
Coronary artery dilatations	2120 (86.0)	1370 (84.7)	750 (88.7)	488 (70.8)	319 (67.6)	169 (77.9)
Coronary artery aneurysms	309 (12.5)	219 (13.5)	90 (10.6)	206 (29.9)	152 (32.2)	54 (24.9)
Giant coronary artery aneurysms	35 (1.4)	29 (1.8)	6 (0.7)	36 (5.2)	32 (6.8)	4 (1.8)
Coronary artery stenosis	6 (0.2)	5 (0.3)	1 (0.1)	6 (0.9)	5 (1.1)	1 (0.5)
Myocardial infarction	4 (0.2)	4 (0.2)	0	1 (0.1)	1 (0.2)	0
Valvular lesions	503 (17.4)	272 (14.7)	231 (22.0)	164 (19.5)	78 (14.3)	86 (29.1)

Values are number (%).
*The total number of patients, including both male and female patients, varies because of missing data.
†Total cardiac complications consisted of CAAs and valvular lesions. CAAs and valvular lesions could develop in the same patient; therefore, total numbers do not match, and percentages do not total 100%.
‡Multiple types of CAAs could develop at the same time point; therefore, the numbers and percentages do not match the total of CAAs and 100%, respectively.

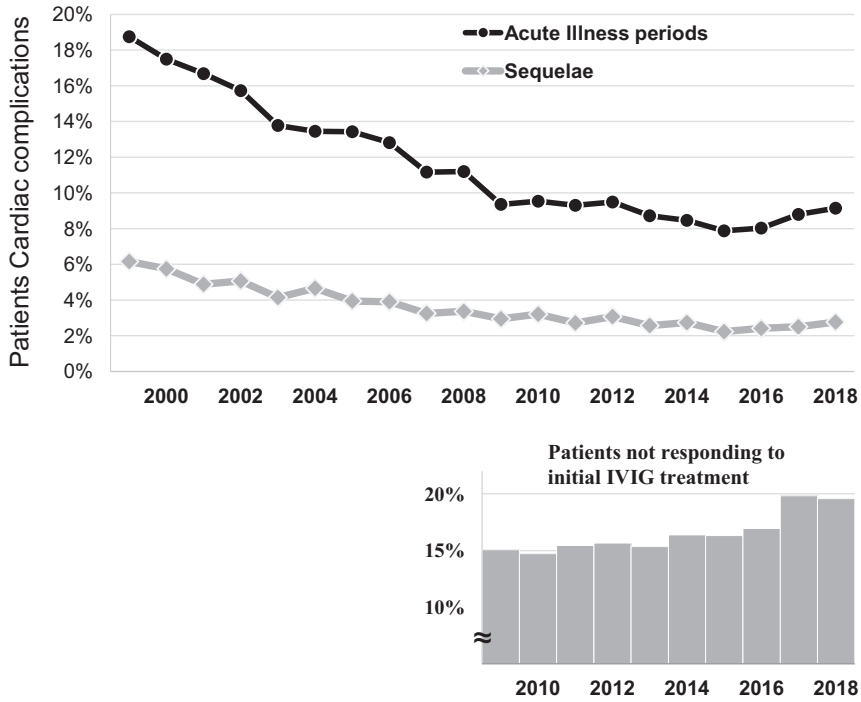

Figure 5. Cardiac complications resulting from Kawasaki disease: the nationwide survey in Japan, 1999-2018. Cardiac complications were recorded as being detected during acute illness (<30 days from the onset of Kawasaki disease) or after acute illness (≥30 days from disease onset, which was defined as cardiac sequelae). Data for initial IVIG nonresponders was available from 2009.

increased percentage of patients diagnosed with ≤4 principal Kawasaki disease signs. Second, the number of etiologic agents for Kawasaki disease might have increased over the survey years, resulting in more patients developing Kawasaki disease, although this is only a hypothesis because the cause of Kawasaki disease remains accurately unidentified. Some previous studies supported that multiple unknown infectious agents might trigger Kawasaki disease onset, although patients' genetic backgrounds might modify disease development.[23-30]

Recent advances in Kawasaki disease treatments could have contributed to preventing the development of cardiac complications. Early initial IVIG administration secondary to early diagnosis of Kawasaki disease could have affected the decreasing trends in the proportion of cardiac complications. CAAs detected at admission could indicate the risk of subsequent coronary outcomes and help inform early treatment as well as initial adjunctive treatments.[19,22] Our survey data indicated that the number of patients receiving standard initial IVIG treatment (2 g/kg/day as a single infusion) increased annually, although the median days of illness at IVIG administration were unchanged (data not shown). In addition, previous studies have reported lower proportions of CAAs in patients with Kawasaki disease receiving primary adjunctive treatments as well as additional treatments for initial IVIG nonresponders, such as the use of corticosteroids, infliximab, or cyclosporin.[31-41]

Patients with Kawasaki disease who do not respond to initial IVIG treatment are at high risk of developing cardiac complications.[42] Our findings indicated that the annual proportions of initial IVIG nonresponders increased slightly after 2015, corresponding to an increasing proportion of cardiac complications. It is difficult to determine why the proportion of patients with Kawasaki disease not responding to initial IVIG administration has recently increased. A previous study focusing on seasonality in Kawasaki disease suggested that the currently unknown etiologic agents of Kawasaki disease might differ between initial IVIG responders and nonresponders, which might support our finding that the percentage of nonresponders increased after 2015.[25] Another possible hypothesis is recent subtle changes in IVIG components because IVIG is derived from human donors, and the mechanism of action of IVIG in Kawasaki disease treatment is unknown.[3]

This study has several limitations. First, although the present and past nationwide Kawasaki disease surveys covered major hospitals throughout Japan where patients with Kawasaki disease were eventually hospitalized and maintained high response rates of >70%, some patients with Kawasaki disease might be admitted and receive treatments in other medical facilities that did not meet the selection criteria in the survey, such as small hospitals and clinics.[10,11] A previous report estimated that the actual number of patients with Kawasaki disease in Japan might be ≤10% higher than the number recorded in the survey.[10] Second, the survey noted CAAs mostly based on the Japanese criteria.[14,15] However, z-score evaluations, the criteria used worldwide, could increase the recognition of CAAs compared with the Japanese criteria.[21,43,44] A preliminary analysis using data from separate survey appending the 25th nationwide Japanese Kawasaki disease survey indicated that ≥34% of patients were evaluated CAAs using z-score

criteria (unpublished data). Further studies should assess the difference between the Japanese and z-score criteria.[21] Third, the surveys did not have information on specific subtypes of valvular lesions. A previous study followed patients with Kawasaki disease registered in the survey and addressed this issue.[45] Finally, the assessment of echocardiogram findings was not standardized or centralized in the survey.

In conclusion, the present study summarized recent epidemiologic and clinical trends in patients with Kawasaki disease in Japan, using data from the nationwide survey. The annual number of patients who developed Kawasaki disease in Japan has increased consistently since 1970, with the highest number in 2018. Conversely, the annual percentage of cardiac complications resulting from Kawasaki disease has decreased in the most recent 2 decades. Early diagnosis of Kawasaki disease as well as advances in initial treatments could explain these findings. ■

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References

1. Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004;364:533-44.
2. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol 2016;67:1738-49.
3. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-99.
4. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi 1967;16:178-222.
5. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974;54:271-6.
6. Nakamura Y, Yanagawa H. The worldwide epidemiology of Kawasaki disease. Prog Pediatr Cardiol 2004;19:99-108.
7. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J 2010;29:483-8.
8. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol 2012;22:79-85.
9. Lin MT, Wu MH. The global epidemiology of Kawasaki disease: review and future perspectives. Glob Cardiol Sci Pract 2017;2017:e201720.
10. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, et al. Epidemiological observations of Kawasaki disease in Japan, 2013-2014. Pediatr Int 2018;60:581-7.
11. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016. Pediatr Int 2019;61:397-403.
12. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int 2005;47:232-4.
13. Guidelines for medical treatment of acute Kawasaki disease: report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). Pediatr Int 2014;56:135-58.
14. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Digest version. Circ J 2014;78:2521-62.
15. Akagi T, Rose V, Benson LN, Newman A, Freedom RM. Outcome of coronary artery aneurysms after Kawasaki disease. J Pediatr 1992;121:689-94.
16. Bratincsak A, Reddy VD, Purohit PJ, Tremoulet AH, Molkara DP, Frazer JR, et al. Coronary artery dilation in acute Kawasaki disease and acute illnesses associated with fever. Pediatr Infect Dis J 2012;31:924-6.
17. Dominguez SR, Anderson MS, El-Adawy M, Glode MP. Preventing coronary artery abnormalities: a need for earlier diagnosis and treatment of Kawasaki disease. Pediatr Infect Dis J 2012;31:1217-20.
18. Muniz JC, Dummer K, Gauvreau K, Colan SD, Fulton DR, Newburger JW. Coronary artery dimensions in febrile children without Kawasaki disease. Circ Cardiovasc Imaging 2013;6:239-44.
19. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. J Am Heart Assoc 2016;5:e003289.
20. Fuse S, Mori T, Kuroiwa Y, Hirakawa S. On what day of illness does the dilatation of coronary arteries in patients with Kawasaki disease begin? Circ J 2017;82:247-50.
21. Burns JC, Hoshino S, Kobayashi T. Kawasaki disease: an essential comparison of coronary artery aneurysm criteria. Lancet Child Adolesc Health 2018;2:840-1.
22. Son MBF, Gauvreau K, Tremoulet AH, Lo M, Baker AL, de Ferranti S, et al. Risk model development and validation for prediction of coronary artery aneurysms in Kawasaki disease in a north American population. J Am Heart Assoc 2019;8:e011319.
23. Rowley AH. Finding the cause of Kawasaki disease: a pediatric infectious diseases research priority. J Infect Dis 2006;194:1635-7.
24. Ozeki Y, Yamada F, Saito A, Kishimoto T, Yashiro M, Makino N, et al. Epidemiologic features of Kawasaki disease distinguished by seasonal variation: an age-specific analysis. Ann Epidemiol 2018;28:796-800.
25. Kido S, Ae R, Kosami K, Matsubara Y, Makino N, Sasahara T, et al. Seasonality of i.v. immunoglobulin responsiveness in Kawasaki disease. Pediatr Int 2019;61:539-43.
26. Burns JC, Shimizu C, Gonzalez E, Kulkarni H, Patel S, Shike H, et al. Genetic variations in the receptor-ligand pair CCR5 and CCL3L1 are important determinants of susceptibility to Kawasaki disease. J Infect Dis 2005;192:344-9.
27. Thornton S. Contribution of angiogenic genes to the complex genetic trait underlying Kawasaki disease. Arthritis Rheum 2006;54:1361-5.
28. Kuo HC, Huang YH, Chien SC, Yu HR, Hsieh KS, Hsu YW, et al. Genetic variants of CD209 associated with Kawasaki disease susceptibility. PLoS One 2014;9:e105236.
29. Huang YH, Hsu YW, Lu HF, Wong HS, Yu HR, Kuo HC, et al. Interferon-gamma genetic polymorphism and expression in Kawasaki disease. Medicine (Baltimore) 2016;95:e3501.
30. Xie X, Shi X, Liu M. The roles of genetic factors in Kawasaki disease: a systematic review and meta-analysis of genetic association studies. Pediatr Cardiol 2018;39:207-25.
31. Inoue Y, Okada Y, Shinohara M, Kobayashi T, Kobayashi T, Tomomasa T, et al. A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome. J Pediatr 2006;149:336-41.
32. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012;379:1613-20.
33. Chen S, Dong Y, Yin Y, Krucoff MW. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. Heart 2013;99:76-82.
34. Sonoda K, Mori M, Hokosaki T, Yokota S. Infliximab plus plasma exchange rescue therapy in Kawasaki disease. J Pediatr 2014;164:1128-32.e1.
35. Chen S, Dong Y, Kiuchi MG, Wang J, Li R, Ling Z, et al. Coronary artery complication in Kawasaki disease and the importance of early intervention: a systematic review and meta-analysis. JAMA Pediatr 2016;170:1156-63.
36. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2017;1:Cd011188.

37. Jone PN, Anderson MS, Mulvahill MJ, Heizer H, Glode MP, Dominguez SR. Infliximab plus intravenous immunoglobulin (IVIG) versus IVIG alone as initial therapy in children with Kawasaki disease presenting with coronary artery lesions: is dual therapy more effective? Pediatr Infect Dis J 2018;37:976-80.
38. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, et al. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health 2018;2:855-62.
39. Nagatomo Y, Muneuchi J, Nakashima Y, Nanishi E, Shirozu H, Watanabe M, et al. Effective infliximab therapy for the early regression of coronary artery aneurysm in Kawasaki disease. Int J Cardiol 2018;271:317-21.
40. Hamada H, Suzuki H, Onouchi Y, Ebata R, Terai M, Fuse S, et al. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. Lancet 2019;393:1128-37.
41. McCrindle BW, Rowley AH. Improving coronary artery outcomes for children with Kawasaki disease. Lancet 2019;393:1077-8.
42. Uehara R, Belay ED, Maddox RA, Holman RC, Nakamura Y, Yashiro M, et al. Analysis of potential risk factors associated with nonresponse to initial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan. Pediatr Infect Dis J 2008;27:155-60.
43. de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 1998;133:254-8.
44. Belay ED, Maddox RA, Holman RC, Curns AT, Ballah K, Schonberger LB. Kawasaki syndrome and risk factors for coronary artery abnormalities: United States, 1994-2003. Pediatr Infect Dis J 2006;25:245-9.
45. Tsuda E, Yashiro M, Nakamura Y. cardiac valvular lesions due to Kawasaki disease: a Japanese nationwide survey. J Pediatr 2020;218:78-84.

50 Years Ago in *The Journal of Pediatrics*

Erythromycin versus Penicillin for the Treatment of Streptococcal Skin Infections

Derrick CW, Dillon HC. Further studies on the treatment of streptococcal skin infections. J Pediatr 1970;27:696-700.

The study of Derrick and Dillon is a well-construed, complex allocation, prospective clinical trial of therapies for streptococcal skin infection in children across 2 July-through-November seasons in Birmingham, Alabama. In 1967, 335 patients with proven streptococcal impetigo were alternately assigned by odd-even medical record numbers to treatment with erythromycin orally 4 times per day for 7 days or a single dose of benzathine penicillin (Bicillin) intramuscularly. In 1968, 373 children were assigned in the same fashion to receive the same erythromycin orally 4 times per day but for 10 days or phenoxymethyl penicillin (Pen VK) orally 3 times per day for 10 days. Primary outcomes (as we would so specify today a priori) would seem to have been clinical cure of impetigo and skin eradication of *Streptococcus pyogenes* at 14 days. Secondary outcomes were the prevalence and impact of therapy on respiratory tract colonization, and "recurrent" streptococcal impetigo in the seeming 6+ weeks of follow-up. Although intuitively a noninferiority trial with benzathine penicillin as the comparator, neither sample size calculations nor statistical bounds of noninferiority were specified.

Cliff Notes on the findings were that (1) clinical cure exceeded 98% in all groups, (2) respiratory tract colonization at entry, which occurred in 12% of patients (likely secondary to impetigo), was "eradicated" at 14 days best by benzathine penicillin, (3) recurrences of impetigo at 3-4 weeks occurred in 3.6%-6.3% of patients across groups, the lowest rate being in the benzathine penicillin group (not statistically significant, although statistics not reported), (4) recurrences after benzathine penicillin tended to occur at 5-6 weeks, and (5) early recurrences tended to be due to the same serotype of *S pyogenes* (relapses), whereas later recurrences tended to be due to new serotypes (reinfections).

An additional caveat was that *S aureus* also was isolated from skin lesions in approximately one-half of cases of streptococcal impetigo, with one-half of *S aureus* isolates resistant to penicillin, but all susceptible to erythromycin. Despite this, all outcomes (ie, cure of impetigo, fate of streptococcal colonization, and recurrence of impetigo) were similar in the penicillin- and erythromycin-treated groups. Compared with earlier studies assessing topical treatment of streptococcal impetigo, which showed that persistence of infection and recurrences were common, any systemic therapy in the Derrick-Dillon trial was clearly superior.

This study figured importantly in what we currently consider to be optimal management of streptococcal impetigo. In the 1960s, the stakes were high as post-streptococcal acute glomerulonephritis was common. In fact, 91 of the 708 study participants in the Derrick-Dillon study were impetigo cases in siblings of patients with poststreptococcal acute glomerulonephritis. One wonders where nephritogenic strains of *S pyogenes* went and why. This was an excellent study and we are grateful for its lessons. Although penicillin effectiveness would still be >98%, expected macrolide performance of 1968 would have to be tempered by current *S pyogenes* resistance rates of 5%-10% in most areas of the US, with some rates as high as 20%.

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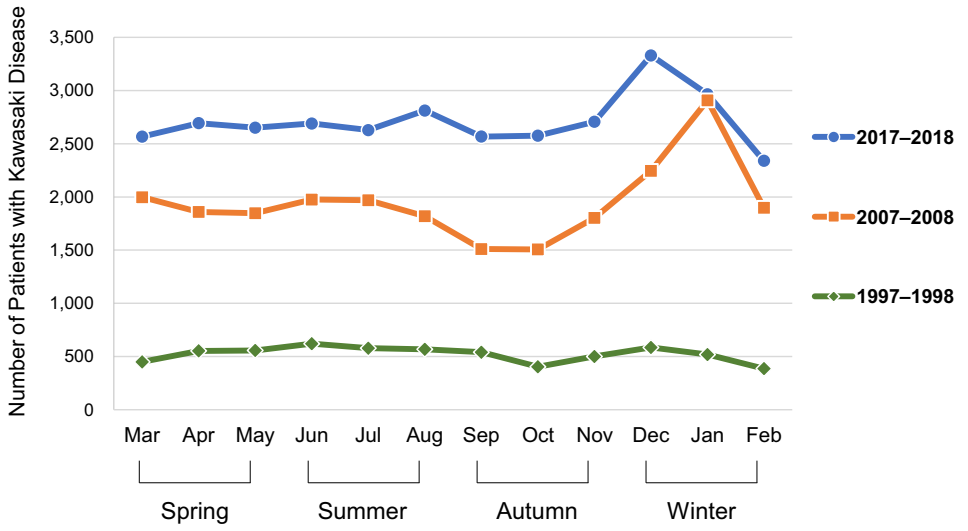

Figure 1. Seasonality of Kawasaki disease in Japan (1997-1998, 2007-2008, and 2017-2018). Note: The total number of patients in 2017-2018, 2007-2008, and 1997-1998 were 32 528, 23 337, and 6257, respectively.

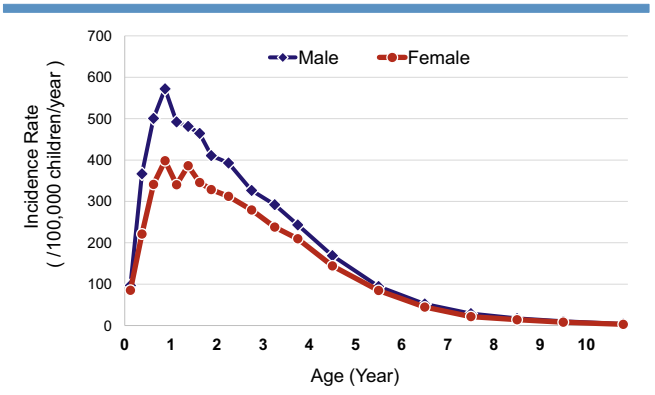

Figure 3. Age-specific incidence rate of Kawasaki disease: the nationwide survey in Japan, 2017-2018.

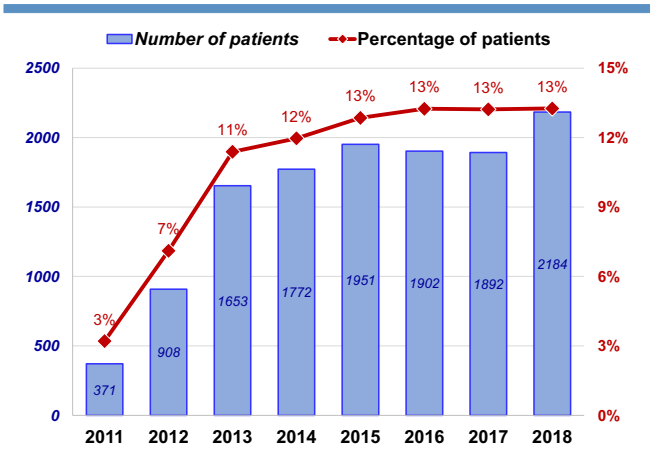

Figure 4. Temporal trends in patients with Kawasaki disease who received corticosteroid combination use with initial IVIG treatment.

Table I. Basic characteristic of patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018 (n = 32 528)

Characteristics	Total (n = 32 528)	Year 2017 (n = 15 164)	Year 2018 (n = 17 364)
Age, mo	27 (14-45)	26 (14-45)	28 (15-46)
<12	6141 (18.9)	2979 (19.6)	3162 (18.2)
12-23	8032 (24.7)	3832 (25.3)	4200 (24.2)
24-35	6213 (19.1)	2870 (18.9)	3343 (19.3)
36-47	4724 (14.5)	2095 (13.8)	2629 (15.1)
48-59	3127 (9.6)	1420 (9.4)	1707 (9.8)
≥60	4291 (13.2)	1968 (13.0)	2323 (13.4)
Sex			
Male	18 599 (57.2)	8635 (56.9)	9964 (57.4)
Female	13 929 (42.8)	6529 (43.1)	7400 (42.6)
Recurrent Kawasaki disease			
+	1478 (4.6)	668 (4.4)	810 (4.7)
–	31 004 (95.4)	14 479 (95.6)	16 525 (95.3)
Sibling history of Kawasaki disease			
+	696 (2.2)	311 (2.1)	385 (2.2)
–	31 634 (97.8)	14 765 (97.9)	16 869 (97.8)
Parental history of Kawasaki disease			
+	419 (1.3)	184 (1.2)	235 (1.4)
–	28 264 (86.9)	13 122 (86.5)	15 142 (87.2)
Unknown	3845 (11.8)	1858 (12.3)	1987 (11.4)
No. of principal signs of Kawasaki disease			
5-6 (complete Kawasaki disease)	25 661 (78.9)	11 945 (78.8)	13 716 (79.0)
4*	5024 (15.5)	2302 (15.2)	2722 (15.7)
1-3*	1823 (5.6)	906 (6.0)	917 (5.3)
Days of illness at admission	4 (3-5)	4 (3-5)	4 (3-5)
1-3	12 487 (38.4)	5824 (38.4)	6663 (38.4)
4-6	17 648 (54.3)	8224 (54.2)	9424 (54.3)
7-9	2057 (6.3)	952 (6.3)	1105 (6.4)
≥10	336 (1.0)	164 (1.1)	172 (1.0)

The sample sizes for the variables vary because of missing data. Values are median (IQR) or number (%).
*Defined as incomplete Kawasaki disease.

Table IV. Cardiac complications developing during acute illness period (<30 d from disease onset) in patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018

Cardiac complications	Total (n = 2885)	Male (n = 1840)	Female (n = 1045)
Total*			
At admission	1587 (55.0)	1027 (55.8)	560 (53.6)
After admission†	1298 (45.0)	813 (44.2)	485 (46.4)
CAAs	(n = 2467)	(n = 1622)	(n = 845)
At admission	1332 (54.0)	893 (55.1)	439 (52.0)
After admission†	1135 (46.0)	729 (44.9)	406 (48.0)
Valvular lesions	(n = 499)	(n = 271)	(n = 228)
At admission	283 (56.7)	154 (56.8)	129 (56.6)
After admission†	216 (43.3)	117 (43.2)	99 (43.4)

Sample sizes are not the same as the total number in Table III (n = 2895) because of missing data. Values are number (%).
*Multiple types of cardiac complications could develop in the same patient; therefore, the total numbers do not match the total number of cardiac complications.
†Without any cardiac complications initially detected at admission.