Reality of the Kawasaki disease epidemiology

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Running title: Kawasaki disease epidemiology
Abstract

Epidemiologic studies of Kawasaki disease (KD) have shown new pattern or change of KD occurrence and supported to infer pathophysiology or risk factors of KD from the first patient with KD reported in 1961. The incidence of KD in Northeast Asia country including Japan, South Korea, China and Taiwan are 10-30 times higher than that of KD in the United States and Europe. Knowing true epidemiology of KD in each country and publications of update KD epidemiology also could give KD vigilance to general health care provider and general population, which definitely could give early detection of KD, early treatment, and finally reduction of coronary artery complications and mortality from KD. Therefore, the effort to investigate true epidemiology of KD should be continued in every country for the quality care of patients with KD using questionnaire survey, national health insurance system data, or combined methods depending on each country’s medical environment.

Keywords: Kawasaki disease, Epidemiology, Seasonal variation, Surveys and questionnaires, National health insurance
Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis which predominantly occurs in the children younger than 5 years of age, and KD is a most common acquired heart disease during childhood in most industrialized countries.\(^1\) Well-known complication of KD is that coronary artery abnormalities, which could occur up to 15–25% of patients if KD is not treated on time.\(^2, 3\) However, the etiology of KD remains unclear until now and many researchers in the world still try to find the exact pathophysiology, genetic profiles and new treatment strategy.

What is the benefit to know the epidemiology of KD in this era? Knowing the true epidemiology of any disease is the basic to understand any specific disease. We also could find new pattern or change of disease occurrence and infer pathophysiology or risk factor of specific disease by knowing true epidemiology. Unfortunately, still a large number of children with KD are being mis-diagnosed as other infectious disease in many developing countries and even in South Korea.\(^4\) Knowing true epidemiology of KD in each country could give KD vigilance to general health care provider including pediatrician and also suggest a clue for KD burden in acute KD treatment setting and long-term adult coronary artery disease from KD.\(^4, 5\) Therefore, the effort to investigate true epidemiology of KD should be continued in every country for the quality care of patients with KD.

The history of KD epidemiology

From the first patient with KD reported in 1961 and 50 patients published in 1967 by Dr. Tomisaku Kawasaki for over 5 years after his first patient, KD was known to the Japanese doctors.\(^6\) From these case series, nationwide epidemiologic survey has begun in Japan since 1970 every 2 years and more than 300,000 patients have been reported until now.\(^7\) After first report of KD in Japan, KD cases have been recognized on every continent by the 1980s.
Nowadays, KD has been reported from more than 60 countries across all continents and has been recognized and published increasingly in developing countries.\textsuperscript{4, 7} In South Korea, nationwide surveys for KD started in 1994 using KD patient data from all the resident-training hospitals between 1991 and 1993, and had been conducted every 3 years.\textsuperscript{8} Taiwan started their national surveillance of KD in 1995 using data collected from national health insurance (NHI) database different from Japan’s and South Korea’s.

\textbf{The Methodology of KD epidemiology}

The method to get epidemiology of KD differ from every country according to each country’s medical environment, therefore, epidemiological comparisons between countries should be considered in view of different epidemiological methods and completeness of diagnostic ascertainment and patient reporting.\textsuperscript{2} Most frequently used method is to use active nationwide survey as like as in Japan and South Korea.\textsuperscript{8, 9} The definite merit of this modality is that we can get various and detailed data of KD occurrence including laboratory data, coronary artery complication, detailed other complications, and etc. from the tailored questionnaire. From the detailed data, we can infer pathophysiology and risk factors of KD occurrence and complications. Most important factors to get accurate incidence are to recruit hospitals to treat KD as many as possible and improve response rate of nationwide survey. The successful survey depends on each hospital’s active participation and principal investigator’s effort to get the data. The response rate in Japan was 71.6\% from the 2011 to 2012 nationwide survey and 74.9\% from the 2013 to 2014 nationwide survey.\textsuperscript{9, 10} In south Korea, the response rate was 87\% from the 2009 to 2011 nationwide survey and 94.8\% from the 2012 to 2014 nationwide survey.\textsuperscript{8, 11} These factors, which affect KD incidence are inborn drawback of nationwide survey. The other problem is that the accurate diagnosis of KD at each hospital could be quite diverse. Some hospitals have a tendency of over-diagnosis of KD.
and some hospitals have a tendency of under-diagnosis of it. Therefore, nationwide survey cannot reflect true incidence of KD despite its traditional value and merit to give clues to get the pathophysiology and risk factors of KD from the diverse data.

The other method to get KD incidence is to use national health insurance system data like in Taiwan and recent South Korea.\textsuperscript{12-15} The necessity to use this system is the strength to cover whole population of each country. Because national health insurance program of Taiwan and South Korea cover greater than 99% of the population of each country due to mandatory subscription, we can guess that we could get the whole incidence of KD treated at all the hospital. In South Korea, they used the data of the patients who received intravenous immunoglobulin under the diagnosis of KD (ICD-10, M30.3).\textsuperscript{13} This method could give much more incidence data of KD compared with nationwide survey method because of its imperfect response rate, however, it is also not free from the possibility of over-diagnosis or under-diagnosis of KD in real practice. And, the demerit of this system is that collected data are mostly simple and usually confined to incidence, age distribution, sex ratio, province distribution, seasonal variation. From the national health insurance data, some patients with KD who did not receive intravenous immunoglobulin could be missed. For example, 4.6% patients with KD were not treated with intravenous immunoglobulin from the nationwide survey data between 2012 and 2014 in South Korea, which means that 4.6% of patients with KD were not included in the national health insurance data.\textsuperscript{8}

There are also other modalities to reveal KD incidence depending on each country’s medical system. For example, in United States, they are using passive national surveillance reporting to the Centers for Disease Control and Prevention, kids’ inpatient database, or nationwide inpatient sample since mid-1970s.\textsuperscript{12,16} In China with huge population, nationwide survey is quite difficult, therefore, they are using each local province questionnaire survey for KD incidence, especially in Beijing and Shanghai\textsuperscript{17}
Global incidence of KD

Diverse epidemiological patterns of KD of each country were described in Table 1 and Figure 1. The incidence of KD is quite different from country to country. The incidence of KD in Northeast Asia country including Japan, South Korea, China and Taiwan are 10-30 times higher than that of KD in the Unites States and Europe.\(^8, 9, 16\) And, the other unique finding is that the incidence of KD is increasing continuously in the Northeast Asia country,\(^8, 9\) however, the incidence of KD is stationary in North America\(^18\) and Europe.\(^16\)

The incidence of KD in Japan is increasing continuously and last incidence of KD was 308 per 100,000 less than 5-year-old in 2014\(^9\) and the incidence of KD in South Korea is also increasing continuously and last incidence of KD was 194.7 per 100,000 less than 5-year-old in 2014 from the nationwide survey\(^8\). In China, epidemiologic study was performed in the Beijing and Shanghai using questionnaire survey, and incidence of KD was reported as 111.6 and 71.9 per 100,000 less than 5-year-old respectively.\(^17\) Taiwan traditionally used national health insurance review for KD epidemiology study and incidence of KD had been known as 82.8 per 100,000 less than 5-year-old in 2010.\(^15\)

Outside Northeast Asia country, the incidence of KD is low significantly. In North America, KD epidemiological studies have been performed using administrative data and incidence of KD in the United States was 19.1 per 100,000 less than 5-year-old in 2015 and those in Canada was 19.6 per 100,000 less than 5-year-old in 2014.\(^18\) Compared with the incidence of KD in the Northeast Asia, the incidence of KD was stationary without significant increase or decrease over several decades\(^4, 16\). Interesting finding of KD epidemiology in the Unites States is that children of Asia-Pacific Islander descent had the highest incidence of KD among ethnic variation. Especially in Hawaii, the incidence of KD in the Japanese Americans
was similar to that in Japan (greater than 200 per 100,000 less than 5-year-old), which suggests an in-depth genetic susceptibility of KD occurrence.\textsuperscript{4,19}

The epidemiologic studies have not been active in the most European countries and the incidence of KD have been reported less than 17.6 per 100,000 less than 5-year-old\textsuperscript{20} and the incidence of KD was stationary without significant increase or decrease like in the North America.\textsuperscript{4,21,22} In Latin America, epidemiological study of KD is no still systematic in each country and KD occurrence have been reported sporadically in several countries.\textsuperscript{23,24}

Recently, the Latin American Kawasaki Disease Network (REKAMLATINA) has been founded and expected to improve the epidemiology of KD in Latin America. Twenty Latin American countries joined in this project and has been using multinational database since 2013.\textsuperscript{25}

\textbf{What KD epidemiology suggest clinical meaning?}

KD epidemiologic studies in each country have shown diverse disease patterns and changes of KD symptoms, signs and laboratories findings for several decades. These historical changes modified the guideline in the diagnostic criteria of Kawasaki disease over times. For example, recent American Heart Association guideline in 2017 suggested that in the presence of greater than 4 principal clinical symptoms, particularly when the patient shows redness and swelling of the hands and feet, the diagnosis of KD may be made with only 4 days of fever.\textsuperscript{2}

And, they also suggested that experienced clinicians who have treated many KD patients may make the diagnosis of KD in rare instances with only 3 days of fever in the presence of a classic clinical symptoms and signs.\textsuperscript{2}

KD epidemiological studies also have shown the grounds of pathophysiology or risk factor for KD. Seasonal variations in each country have been the major findings of KD epidemiology. Regions in the extratropical northern hemisphere including Japan, South Korea,
and Unites States have peaks of KD incidence in the winter season and second peak in summer season in Japan and South Korea, spring season in Unites States.\textsuperscript{2, 8, 9, 19} There has been a lack of a seasonal variation in the tropics and the extratropical southern hemisphere.\textsuperscript{2} Several epidemiological studies demonstrated that KD is associated with preceding respiratory illness.\textsuperscript{2, 26, 27} The other important fact in the KD epidemiology has been that KD occurs predominantly in the Northeast Asia and Japanese Americans also showed high incidence in the Unites States like in Japan\textsuperscript{4, 19} These two unique findings in the KD epidemiological studies of seasonal variation and geographical patterns of KD occurrence have been suggested that many infectious agent activates innate and adaptive immune system and provoke KD in genetically susceptible patient.\textsuperscript{2, 7, 28} Knowing true epidemiology of KD in each country and publications of update KD epidemiology also could give KD vigilance to general health care provider including general practitioner, pediatrician and parents of patients with KD. KD vigilance in the general health care provider and general population definitely could give early detection of KD and early treatment, which could reduce coronary artery complications and mortality.\textsuperscript{4, 5} For example, the percentage of giant aneurysm decreased from 0.26\% in the 2009-2011 nationwide survey to 0.16\% in the 2012-2014 nationwide survey in South Korea accompanied with the increased KD incidence.\textsuperscript{8, 11}

**What could be the best epidemiological study of KD?**

As above-mentioned, the success of epidemiological study depends on the completeness of KD diagnostic ascertainment and patient reporting. For the nationwide survey for the KD, most important point for correct investigation is to get 100\% response rate from all the hospitals to treat acute KD. However, getting 100\% response rate from the whole hospitals is
inevitably impossible in the real world because nationwide survey needs each hospital’s very active participation. For the epidemiological study using national health insurance system data, most critical point for correct investigation is to recruit all the KD patients with or without intravenous immunoglobulin treatment and to gather epidemiologically detailed data as many as possible to overcome the diversity of nationwide questionnaire survey.

For the basic epidemiological data including KD incidence, age, sex distribution, and seasonality, epidemiological study using national health insurance system would be the best modality if we could search all the KD patients from the national data in case of mandatory subscription of national health insurance system. For the detailed epidemiologic data including each patient’s symptoms, signs, laboratories findings, echocardiographic finding, and other combined morbidities, nationwide questionnaire survey has strong benefit to show disease changes and possible pathogenesis of KD. Therefore, these two epidemiologic modalities should be combined to reveal true epidemiology of KD.

**Conclusions**

Epidemiological studies of KD have shown new pattern or change of KD occurrence and supported to infer pathophysiology or risk factors of KD. Therefore, the effort to investigate true epidemiology of KD should be continued in every country for the quality care of patients with KD using questionnaire survey, national health insurance system data, or combined methods depending on each country’s medical environment.

**Conflicts of interest:** None
References


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* Presented at the 12th international Kawasaki disease symposium, 2018

# Incidence per 100,000 less than 18-year-old

NA; non-applicable
Figure legend

Figure 1 (Graphic abstract)

Incidence of Kawasaki disease in the world. The incidence of Kawasaki disease (KD) has various geographic occurrence pattern. The incidence of KD is much higher in Northeast Asia country including Japan, South Korea, China and Taiwan, which is 10-30 times higher than that of KD in the North America and Europe.