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# Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin☆

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ABSTRACT

*Backgrounds:* Kawasaki disease (KD) is a systemic vasculitis of childhood involving coronary arteries. Treatment for intractable cases at a higher risk of cardiac sequelae remains controversial.
*Methods:* Clinical outcomes of KD patients diagnosed in Yamaguchi prefecture, Japan between 2003 and 2014 were analyzed using the medical records from all 14 hospitals covering the prefecture. The study included 1487 patients (male:female, 873:614; median age at diagnosis, 24 months).
*Results:* The proportion of initial intravenous immunoglobulin (IVIG)-resistant patients increased from 7% to 23% during this decade, although no patients died. Twenty-four patients developed coronary artery lesions (CALs) over one month after the KD onset. The incidence of CAL in patients who received corticosteroid during the disease course (10/37; 27.0%) was higher than that in those who did not (14/1450; 0.97%, $p = 2.0 \times 10^{-35}$). Nine patients who responded to initial IVIG plus corticosteroids had no CAL. Conversely, IVIG-resistant patients with alternate corticosteroid therapy more frequently developed CAL than those without it (10/28; 35.7% *vs.* 5/194; 2.6%, $p = 8.9 \times 10^{-10}$). Multivariate analyses indicated corticosteroid therapy ($p < 0.0001$), hyperbilirubinemia ($p = 0.0010$), and a longer number of days before treatment ($p = 0.0005$) as risk factors associated with CAL over a month after onset. The odds ratio of corticosteroid use increased from 18.3 to 43.5 if the cases were limited to initial IVIG non-responders and corticosteroid free-IVIG responders.
*Conclusions:* IVIG-failure has recently increased. The incidence of CAL increased in intractable cases with prolonged corticosteroid use. Corticosteroid may not be alternate choice for IVIG-failure to reduce the risk of cardiac sequelae.



## 1. Introduction

Kawasaki disease (KD) is an acute febrile illness with systemic vasculitides that primarily affects infants and young children [1,2]. The critical complication of KD is coronary arterial lesions (CALs), which mostly develop within the first 10 days of illness and are associated with the late complications of myocardial infarction [3]. High-dose intravenous immunoglobulin (IVIG) and aspirin have been established as the first-line therapy for KD to control inflammation and reduce the risk of CALs [4–7]. Conversely, 10–20% of KD patients have a persistent or recrudescent fever lasting more than 36–48 h after the end of initial IVIG infusion [8,9]. These patients refractory to a single dose of IVIG are at a higher risk of CALs than the responders. Recent studies have focused on determining the predictive factors for initial IVIG-resistance [10,11] and adjunctive anti-cytokine therapies to reduce the risk of cardiac sequelae [12,13]. Clinical trials and meta-analyses demonstrated that the addition of corticosteroids to IVIG is beneficial for the prevention of coronary artery aneurysms in severe cases with the highest

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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risk of IVIG-resistance [14,15]. On the other hand, the evidence does not provide clear guidance on which corticosteroid regimen is most effective for the disease control and coronary outcomes [8,16]. Clinical scores to predict IVIG-resistance are suboptimal outside of Japan [17].

KD is the leading cause of acquired pediatric heart disease in developed countries [18,19], although the incidence rates in North East Asians are up to 20 times higher than that of Caucasians. Although the etiology of KD remains unknown, it may be caused by an infectious agent that precipitates an excessive auto-inflammation in genetically predisposed individuals. The nationwide surveys of Japan [19] and Taiwan [20] revealed similar annual increases, seasonal clustering and outbreaks of KD. According to the epidemiology, the densely cultivated region of northeastern China has been recently reported to act as a source for the wind-borne agent of KD [21]. It remains unclear whether the disease severity and treatment outcomes have changed in the accumulating number of patients. Long-term analyses would provide a clue to the management of intractable cases.

In this study, we surveyed the epidemiology of KD in a prefecture of Japan, and investigated the treatment outcomes focusing on the refractory cases according to the information collected from all pediatric hospitals thought the prefecture.

## 2. Patients and methods

### 2.1. Subjects

This study included 1487 children with KD diagnosed and treated in all 14 hospitals in Yamaguchi prefecture, Japan between January 2003 and December 2014. No other hospitals engaged in pediatric inpatient cares in the prefecture, locating at the western edge of the main island, covering 6110.9 $km^2$ and containing a population of 1,445,702. Anonymized data in the prefecture were extracted from the population (1968–2012) in the KD registry of Japan [19]. Each hospital confirmed the medical records during the period 2003–2014. The database was screened for the exclusion of duplicated or inaccurate cases. The diagnosis of KD was made according to the 5th revision of the Diagnostic Guidelines [22]. In twice or more affected patients, the first KD episode was analyzed. Clinical variables were collected from the available data including age, sex, days until diagnosis, type of KD, predicting scores of IVIG-resistance at the diagnosis, development of CAL, treatments and outcomes. KD was classified into two disease types; complete KD was defined in patients who fulfilled 5 or 6 of the major 6 symptoms or those with 4 of the 6 diagnostic symptoms who had a coronary artery aneurysm, as confirmed by coronary angiography or two-dimensional echocardiography, during the disease course. The incomplete type was defined in patients who did not fulfill the diagnostic criteria, but were suspected as having KD. In this study, "CALs" were defined as dilatations or aneurysms of the coronary artery that persisted for more than one month after the KD onset, assessed by echocardiography. Patients received oral aspirin (30 mg/kg daily), IVIG (1–2 g/kg), corticosteroid, infliximab, plasma exchange (PE) and/or immunosuppressive therapy. Failure to respond to IVIG was defined as persistent or recrudescent fever (≥37.5 °C) at 36 h after completion of the initial treatments [8]. Patients with repeated IVIG-failure and/or the formation of "CALs" were managed in 3 tertiary centers (Yamaguchi University Hospital, Iwakuni Clinical Center, and Saiseikai Shimonoseki General Hospital). Corticosteroids were administered in 25 patients who did not respond to repeated IVIG, 6 patients who received RAISE-protocol [16], 6 patients suspected as having allergic disorders. This observational, retrospective and multicenter study was approved by the Institutional Review Board at Yamaguchi University Hospital (H27-173).

### 2.2. Statistical analysis

Differences between the two groups were analyzed using the Mann–Whitney U-test, the chi-square test, or Fisher's exact probability test. An analysis of covariance was used to compare the slope index of regression equations. Spearman's rank-sum test was used for the association study. A multiple logistic regression analysis was performed to analyze factors potentially associated with the CALs. The factors examined as explanatory variables were sex, age, the status of complete or incomplete KD, days until diagnosis, IVIG, times of IVIG, days until the first treatment, the status of treatment with corticosteroids, infliximab, cyclosporine-A, or PE, the prognostic indices: Kurume [23], Gunma [24], and Osaka scores [25], and the laboratory test results: complete blood counts, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein, and sodium levels. The laboratory results with skewed distributions were transformed logarithmically for analysis. The optimal combination of explanatory variables was chosen by the use of a stepwise selection method. These statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 12.0 (SPSS, Chicago, IL).

## 3. Results

### 3.1. Epidemiology of KD

The original database identified 3828 KD cases in Yamaguchi prefecture between 1968 and 2014 (Fig. 1). These cases consisted of 2227 males and 1601 females, median age 22 months (range, 0 to 198 months). Ninety-one of 3665 patients (2.5%) had recurrent KD (2 times: 87 patients, 3 times: 4 patients). Nine patients (0.25%) died of KD. The number of patients increased with two outbreaks in 1982–83 and 1986–87 (Supplementary Fig. 1). The annual incidence was estimated to increase from 3.7 of 1000 births/year (1970–2002) to 10.8 of 1000 births/year (2003–2014), according to the population survey reports of the prefecture.

### 3.2. Treatment modality and initial IVIG responses

The treatment outcomes of 1487 patients between 2003 and 2014 were studied. Demographics of the study population are shown in Table 1, Group A. A total of 1487 patients (873 males, 614 females) developed 1158 (77.9%) complete and 329 (22.1%) incomplete KD. The median age at diagnosis was 24 months (range, 1 to 198 months). Aspirin, IVIG, corticosteroid, infliximab, and PE were administered in 100%, 88.0%, 2.5%, 2.3%, and 0.4% of patients, respectively. No one died of KD between 2003 and 2014. Twenty-four patients (1.6%) presented CALs over a month after the onset of KD.

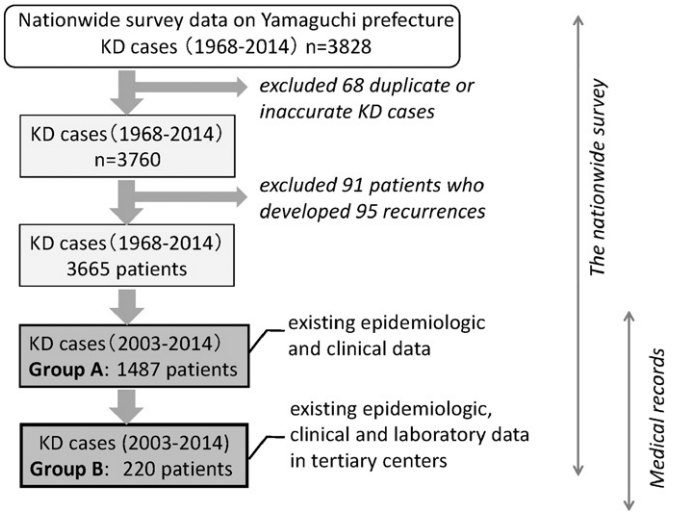


**Fig. 1.** Flowchart of the epidemiological and clinical study on patients with Kawasaki disease (KD) in Yamaguchi prefecture, Japan.