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# Status of treatment and outcome in Kawasaki disease in the Kinki area of Japan

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## Abstract

**Background:** The treatment guidelines for acute Kawasaki disease (KD) have been revised several times. Moreover, the criterion used to define coronary artery abnormalities (CAAs) has changed from the coronary artery's internal diameter to the *Z*-score. Treatment for KD and methods for evaluating CAAs vary between hospitals, so we investigated the actual status of acute KD treatment and development of CAAs under the 2012 Japanese treatment guidelines for acute KD.

**Methods:** The 24th Japanese Nationwide Survey on Kawasaki Disease yielded 2618 patients who developed KD in the Kinki area in 2016. We sent a secondary questionnaire to each participating hospital and used the resulting data to investigate the frequency of CAAs according to *Z*-score, treatment by KD treatment stage, and predictors of CAAs.

**Results:** The response rate was 80.0%. The data for 1426 patients without major data deficiencies were examined. The frequency of CAAs was 3.0% when based on coronary artery internal diameters and 8.8% when based on *Z*-scores. Intravenous immunoglobulins combined with corticosteroids were administered as an initial treatment in 12.8% of cases and as a second-line treatment in 16.8% of cases. Corticosteroids, cyclosporine A, infliximab, and plasma exchange were used at similar frequencies for third-line treatment. A pretreatment maximum coronary artery *Z*-score of ≥1.9 and age <1 year were associated with significantly higher incidences of CAAs.

**Conclusions:** Using the *Z*-score resulted in a threefold increase in the number of patients diagnosed with CAAs. A pretreatment maximum coronary artery *Z*-score of ≥1.9 and age <1 year are useful predictors of CAAs.

**KEYWORDS**
acute treatment, coronary artery abnormality, epidemiology, Kawasaki disease, *Z*-score

  

## INTRODUCTION

Kawasaki disease (KD) develops in more than 15,000 children annually in Japan.[1] Cardiac damage occurs in the early acute phase in approximately 8% of affected individuals, whereas coronary artery abnormalities (CAAs) occur as sequelae in approximately 2.5%.[1] Since the treatment guidelines for acute KD were first published by the Japanese Society of Pediatric Cardiology and Cardiac Surgery in 2003,[2] clinical trials on the use of corticosteroids (the Randomised controlled trial to assess immunoglobulin plus steroid efficacy for kawasaki disease (RAISE) study),[3] infliximab,[4] and cyclosporine A (CsA) (the Multicenter, randomized, open-label study to compare immunoglobulin to immunoglobulin plus cyclosporin A combination therapy in patients with severe Kawasaki disease (KAICA) trial)[5] have been conducted. These treatments, together with plasma exchange therapy,[6] have been added to the 2012 treatment guidelines for acute KD[7] as options for patients who are unresponsive to initial intravenous immunoglobulin (IVIG) treatment. Initial treatment with IVIG and corticosteroids in patients with severe KD was added to the 2012 treatment guidelines for acute KD[7] with the goal of reducing the incidence of CAAs. Furthermore, initial treatment with IVIG and CsA (the KAICA trial) was also added to the revised edition of the 2020 guidelines.[8]

Coronary artery abnormalities are the most serious complications of KD. Until recently, CAAs have been diagnosed on the basis of the internal diameter of the coronary artery.[9,10] However, CAAs are now diagnosed using the *Z*-score, which considers sex and body surface area.[11] It was therefore expected that the frequency and severity of CAAs would vary significantly depending on which of these criteria were used. In addition, treatments vary between hospitals, and the effectiveness with which various treatments suppress CAAs in clinical practice has not been sufficiently investigated.

In this study, we administered secondary questionnaires to hospitals in the Kinki area to further assess the cases reported in the 24th Japanese Nationwide Survey of Kawasaki Disease (January 1, 2015 to December 31, 2016).[12] We examined the following four points: (1) actual KD treatment in clinical practice; (2) variations in the frequency of CAAs between use of the two diagnostic criteria (internal coronary artery diameter vs. *Z*-score); (3) variations in the frequency of CAAs associated with actual treatment protocols; and (4) predictors of development of CAAs as determined by the secondary survey of the 24th Japanese Nationwide Survey of Kawasaki Disease.

## METHODS

In the 24th Japanese Nationwide Survey of Kawasaki Disease (2015–2016),[12] 15,272 patients with KD were registered in Japan from January 1, 2016 to December 31, 2016. Of these, 2618 patients were diagnosed with, and treated for, KD in the Kinki area, which covers the Osaka, Kyoto, Shiga, Nara, Hyogo, Mie, and Wakayama prefectures. For the purpose of this study, the research secretariat sent secondary questionnaires to all hospitals that had participated in the 24th Japanese Nationwide Survey of Kawasaki Disease in the Kinki area. The protocol for this study was approved by the ethics review board of Wakayama Medical University (No. 2245). The study protocol conformed to the principles outlined in the 1975 Declaration of Helsinki. Opt-out for this research was completed on the homepage of Wakayama Medical University (https://www.wakayama-med.ac.jp/topics/rinshoukenkyu/pdf/optout2245a.pdf).

First, we classified the identified patients into an analysis group (valid data in the secondary questionnaires) and a missing data group (missing data on body mass index, coronary artery diameter, and KD treatment). To determine the characteristics of the analysis group, we compared the primary survey data of the analysis and missing data groups using data that had already been obtained in the 24th Japanese Nationwide Survey of Kawasaki Disease. Next, we compared the items investigated in the secondary survey in the analysis group. The items assessed in this study included height, weight, treatment, and maximum diameter of the four coronary artery branches – right coronary artery (C1), left coronary artery main trunk (C5), left anterior descending coronary artery (C6), and left circumflex coronary artery (C11) – before KD treatment and on the 30th day after KD onset. To clarify the clinical features, the time since diagnosis of KD was classified into three groups (1–3, 4,5, and ≥6 days). Blood tests were performed during KD treatment to determine the highest white blood cell count, highest neutrophil count, highest neutrophil ratio, lowest platelet count, highest C-reactive protein concentration, highest aspartate transaminase concentration, highest alanine transaminase (ALT) concentration, highest total bilirubin (TB) concentration, and lowest serum sodium concentration. Patients requiring additional KD treatment were defined as non-responders. Treatment was divided into three stages (initial, second-line, and third-line treatment). Aspirin and flurbiprofen were not considered as KD treatment. The body surface area was calculated using Haycock's equation. The diameters of C1, C5, C6, and C11 were measured on the day before treatment and on the 30th day after KD onset. *Z*-scores were calculated retrospectively using a *Z*-score calculator (version 4.0 full, LMS_*Z*_Score).[13,14] The maximum *Z*-score for each coronary artery branch before KD treatment was defined as "pre-*Z*-max." The internal lumen diameter criterion of the Japanese Ministry of Health (JMH criteria)[9] was used as the old criterion for diagnosing CAAs, whereas the *Z*-score criterion of the American Heart Association[11] was used as the new criterion. We then investigated the distribution of pre-*Z*-max

and examined the relationship between pre-*Z*-max and development of CAAs by the 30th day after KD onset. Finally, to identify predictors of CAAs, we examined the relationships between CAAs and blood test results, age, sex, pre-*Z* max, and treatment administered.

### Statistical analysis

Continuous variables are presented as median (interquartile range), and categorical variables as frequency (percentage). Comparisons were made using the Mann–Whitney *U*-test, the $\chi^2$ test, or the Fisher's exact test, as appropriate. Multivariable logistic regression was used to identify independent predictors of CAA development. A predictor of pre-*Z*-max for CAA development was determined by receiver operating characteristic (ROC) curve analysis. The odds ratios and 95% confidence intervals for the timing of corticosteroid use (no steroid used, initial treatment only, initial + additional treatment, or additional treatment only) for CAAs were calculated using logistic regression models. All statistical analyses were performed using JMP Pro software, version 13 (SAS Institute Japan, Tokyo, Japan). A $p$ value of <0.05 was considered to denote statistical significance.

## RESULTS

### Patients' background characteristics

The secondary questionnaire was responded to by 138 of 172 hospitals (80.2%) and included data for 2095 of 2618 patients (80.0%). Primary data were missing from the secondary questionnaire in 669 of 2095 patients (62 patients: no query description; 452 patients: no data on body mass index; 152 patients: no data on coronary artery diameter; three patients: no data on KD treatment); thus, the final analysis group included 1426 patients (Figure 1). There were no differences in patients' background characteristics (excluding patients with typical and incomplete KD, initial non-responders, initial non-responders treated only with IVIG, and patients who received immunosuppressants as an additional treatment) between the analysis ($n$ = 1426 patients) and missing data groups ($n$ = 1192) (Table 1). The missing data group ($n$ = 1192) included 523 patients for whom no response was received and 669 with missing primary data in the secondary questionnaire. Compared with the missing data group, the analysis group ($n$ = 1426) included a smaller proportion of patients with incomplete KD, whereas it included a greater proportion of non-responders, patients with IVIG only as initial treatment, and patients who received immunosuppressants as additional treatment. The number of patients with CAAs according to the JMH criteria did not differ between the two groups (Table 1). The median number of days at which KD was diagnosed was 4 (3–5) in the overall cohort, 3 (2–5) in patients aged <1 year, 4 (3–5) in patients aged 1 to 5 years, and 4 (3–5) in patients aged ≥5 years (data not shown).

### Differences in treatment by stage

In terms of initial treatment, 1145/1426 patients (80.3%) were treated with IVIG monotherapy, 99/1426 (6.9%) with IVIG combined with intravenous or oral prednisolone, and 83/1426 (5.8%) with IVIG combined with methylprednisolone pulse therapy. The proportion of patients

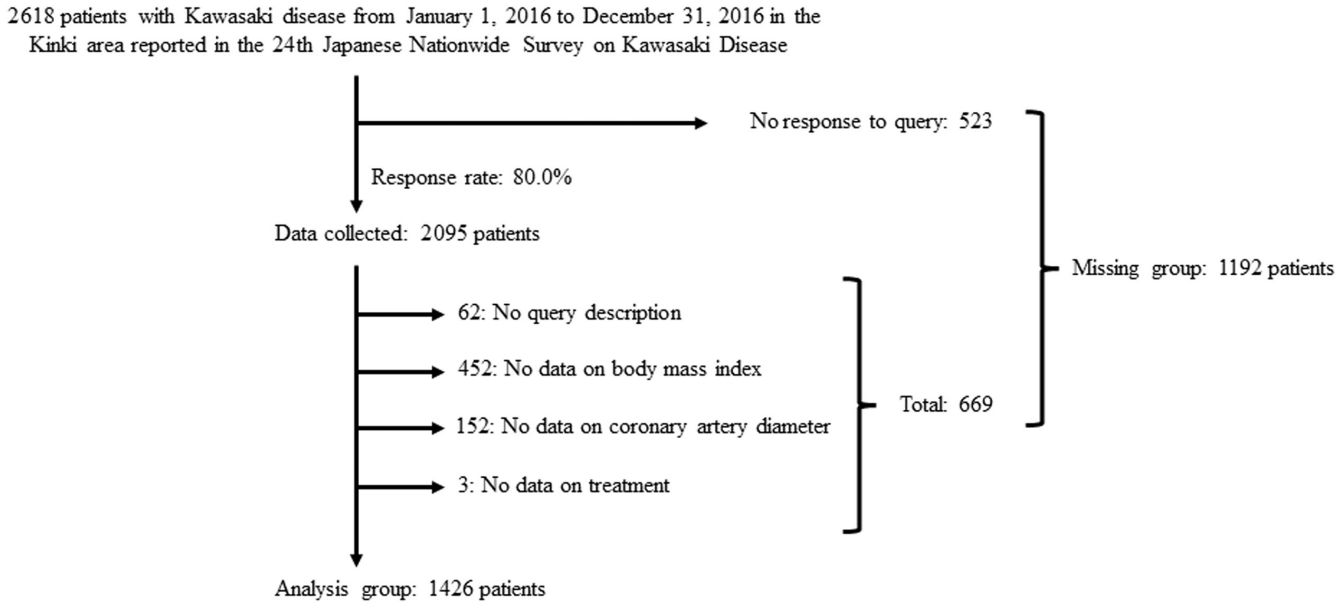


**FIGURE 1** Flowchart of patient recruitment

**TABLE 1** Patients' characteristics

| Characteristics | Analysis group $n = 1426$ | Missing data group $n = 1192$ | $p$ |
|---|---|---|---|
| Age, months | 27 (13–45) | 25 (13–44) | 0.1916 |
| <12 | 299 (20.97) | 255 (21.39) | 0.8102 |
| 12–23 | 333 (23.35) | 297 (24.92) | 0.3588 |
| 24–35 | 258 (18.09) | 231 (19.38) | 0.4205 |
| 36–47 | 205 (14.38) | 160 (13.26) | 0.4269 |
| 48–59 | 140 (9.82) | 101 (8.47) | 0.2489 |
| ≥60 | 191 (13.39) | 150 (12.58) | 0.5601 |
| Sex | | | |
| Male | 775 (54.35) | 690 (57.89) | 0.0753 |
| Female | 651 (45.65) | 502 (42.11) | |
| Number of principal signs of KD | | | |
| Typical | 1116 (78.26) | 878 (73.66) | 0.0066 |
| Atypical | 49 (3.44) | 36 (3.02) | 0.5812 |
| Incomplete | 261 (18.0) | 278 (23.32) | 0.0016 |
| Days since diagnosis of KD | | | |
| 1–3 | 545 (38.22) | 476 (39.93) | 0.3763 |
| 4–6 | 786 (55.12) | 649 (54.45) | 0.7525 |
| 7–9 | 83 (5.82) | 58 (4.87) | 0.2976 |
| ≥10 | 12 (0.84) | 9 (0.76) | 0.8302 |
| Initial IVIG administration | | | |
| None | 78 | 80 | 0.1883 |
| IVIG only | 1166 | 946 | 0.1236 |
| IVIG combined with corticosteroids | 182 | 166 | 0.3865 |
| Days of illness at initial IVIG administration | 4 (3–5) | 4 (3–5) | 0.8108 |
| Initial IVIG non-responders | 297 (20.83) | 199 (16.69) | 0.0079 |
| IVIG only | 251 (21.52) | 158 (16.70) | 0.0024 |
| IVIG combined with corticosteroids | 42 (23.08) | 41 (24.70) | 0.5025 |
| Additional treatments after initial IVIG | | | |
| Additional IVIG | 291 (20.41) | 208 (17.45) | 0.0577 |
| Corticosteroids | 82 (5.75) | 83 (6.96) | 0.2258 |
| Infliximab | 18 (1.26) | 12 (1.01) | 0.5846 |
| Immunosuppressive drugs | 47 (3.30) | 16 (1.34) | 0.0012 |
| Plasma exchange | 14 (0.98) | 10 (0.84) | 0.8376 |
| Coronary artery abnormalities[a] | 43 (3.02) | 36 (3.02) | 1.000 |
| Coronary artery dilation[a] | 32 (2.24) | 27 (2.27) | 1.000 |
| Coronary artery aneurysm[a] | 9 (0.63) | 8 (0.67) | 1.000 |
| Giant coronary artery aneurysm[a] | 2 (0.14) | 1 (0.08) | 1.000 |

*Note*: Data are presented as median (interquartile range), *n* (%), or *n*. Comparisons were performed using the $\chi^2$ test or the Fisher's exact test. The target group and exclusion group were compared using data obtained from the 24th nationwide survey in Japan. The exclusion group ($n = 1192$) comprised 523 patients for whom no response was received and 669 patients with missing primary data (62 patients: no query description, 452 patients: no data on body mass index, 152 patients: no data on coronary artery diameter, three patients: no data on KD treatment).

Abbreviations: IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

[a]Coronary artery abnormalities defined by the internal lumen diameter criterion (JMH criteria).

who received a combination of steroids and IVIG therapy as initial treatment was 12.8% (Figure 2a).

A total of 297/1426 patients (20.8%) did not respond to initial treatment and were thus given second-line treatment. Of these patients, 216/297 (72.7%) were treated with IVIG monotherapy, 21/297 (7.1%) with IVIG therapy combined with intravenous or oral prednisolone, and 22/297 (7.4%) with IVIG combined with methylprednisolone pulse therapy, 16 of whom also received ulinastatin. The proportion of patients who received corticosteroids as second-line treatment was 16.8%, which is higher than for initial treatment (Figure 2b).

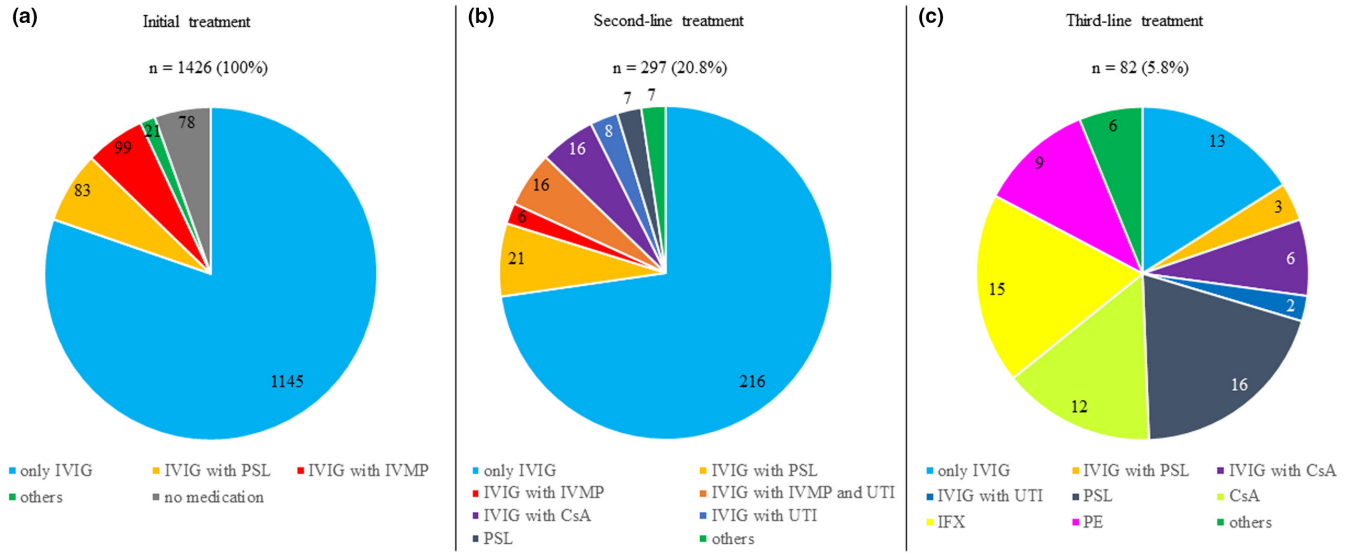


**FIGURE 2** Classification of Kawasaki disease treatment within each treatment line. Numbers in segments indicate patient numbers treated with the specified treatment protocol. Intravenous immunoglobulin was administered as an initial treatment to 1145/1426 patients (80.3%). (a) Corticosteroids combined with IVIG therapy were administered as initial treatment to 182/1426 (12.8%). Second-line treatment was administered to 297/1426 patients (20.8%). (b) IVIG monotherapy was administered to 216/297 patients (72.7%) and corticosteroids to 50/297 patients (16.8%), which is greater than for initial treatment; 82/1426 patients (5.8%) received third-line treatment. (c) Corticosteroids or IVIG + corticosteroids were administered to 19/82 (23.2%) patients, CsA or IVIG + CsA to 18/82 patients (22.0%), infliximab to 15/82 patients (18.3%), and plasma exchange to 9/82 patients (11.0%). CsA, cyclosporine A; IFX, infliximab; IVIG, intravenous immunoglobulin; IVMP, pulsed intravenous methylprednisolone; PE, plasma exchange; PSL, prednisolone; UTI, ulinastatin.

**TABLE 2** Differences in number of patients with CAAs according to criterion used to diagnose these abnormalities

| | JMH criteria | *Z*-score criteria |
|---|---|---|
| CAAs | 43 (3.0) | 126 (8.8) |
| Small coronary artery aneurysm | 32 (2.2) | 114 (8.0) |
| Coronary artery aneurysm | 9 (0.6) | 10 (0.6) |
| Giant coronary artery aneurysm | 2 (0.1) | 2 (0.1) |

*Note*: Data are presented as *n* (%). JMH criteria: (1) Small coronary artery aneurysm: inner diameter 3–4 mm (<5 years of age); (2) Coronary artery aneurysm: inner diameter 4–8 mm; (3) Giant coronary artery aneurysm: inner diameter >8 mm. *Z*-score criteria: (1) Small coronary artery aneurysm: ≥2.5 to <5.0 mm; (2) Coronary artery aneurysm: ≥5.0 to <10.0 mm; (3) Giant coronary artery aneurysm: ≥10 mm.

Abbreviations: CAAs, coronary artery abnormalities; JMH, Japanese Ministry of Health.

A total of 82/1426 patients (5.8%) did not respond to second-line treatment and were thus given third-line treatment. The third-line treatment regimens were more diverse than the initial and second-line regimens. Only 13/82 patients (15.9%) were treated with IVIG monotherapy, whereas 19/82 (23.2%) were treated with corticosteroids or IVIG therapy with corticosteroids. A total of 18/82 patients (22.0%) were treated with CsA or IVIG therapy with CsA, 15/82 (18.3%) with infliximab, and 9/82 (11.0%) with plasma exchange. The other treatments, shown in Figure 2c, varied with some of these patients being treated with combination corticosteroid and immunosuppressant and/or IVIG therapy (Figure 2c).

## Number of CAAs according to the criteria used to define these abnormalities

On the 30th day after KD onset (30 days [28-40 days]), 43/1426 patients (3.0%) were diagnosed as having CAAs when the internal lumen criterion (JMH criteria) was used to define these abnormalities. However, many more patients, 126/1426 (8.8%), were diagnosed as having CAAs when the *Z*-score criterion was used to define them (*Z*-score of ≥2.5). In particular, significantly more patients were diagnosed with small CAAs on the basis of the *Z*-score (2.5 ≤ *Z*-score <5.0) than when this diagnosis was based on the internal lumen diameter criterion (Table 2).

## Relationship between pre-*Z*-max and CAA onset

We constructed the ROC curve for pre-*Z*-max and CAAs because previous research[15–17] has indicated that the pre-*Z*-max is a predictor of development of CAAs. There was no significant difference in the distribution of pre-*Z*-max between the three groups (1–3, 4–5, and ≥6 days) (data not shown). However, there was a weak positive correlation between pre-*Z*-max and coronary artery diameter on the 30th day after KD onset (Figure 3). The area under the ROC curve for pre-*Z*-max and CAAs was 0.748, and the cut-off value for pre-*Z*-max was 1.9 (sensitivity: 61.1%; specificity: 77.9%) according to American Heart Association criteria.

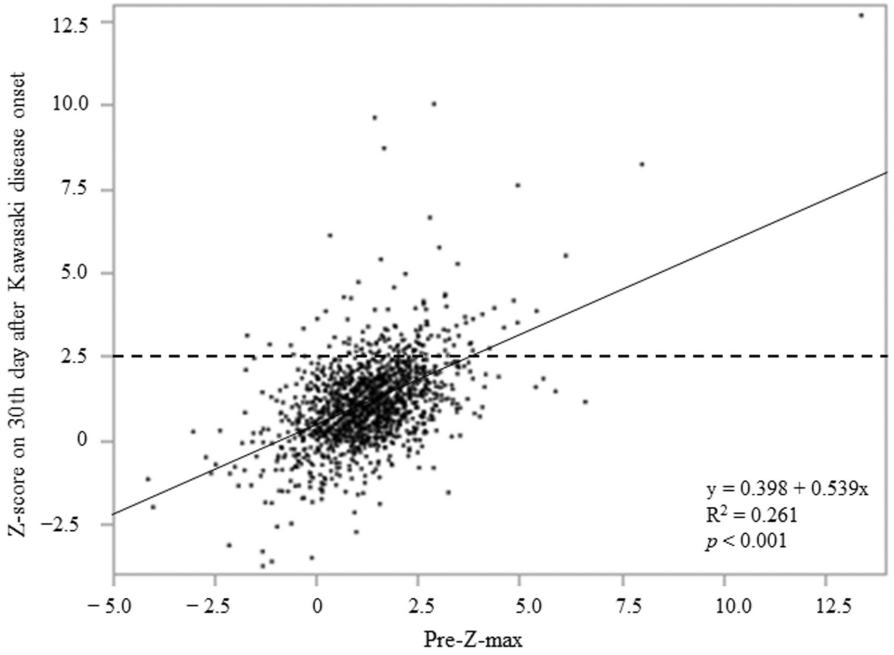


**FIGURE 3** Relationship between pre-*Z*-max and post-*Z*-max scores. There was a weak positive correlation between pre-*Z*-max and coronary artery *Z*-scores on the 30th day after Kawasaki disease onset. Pre-*Z*-max, maximum coronary artery *Z*-score for each coronary artery branch before treatment of Kawasaki disease.

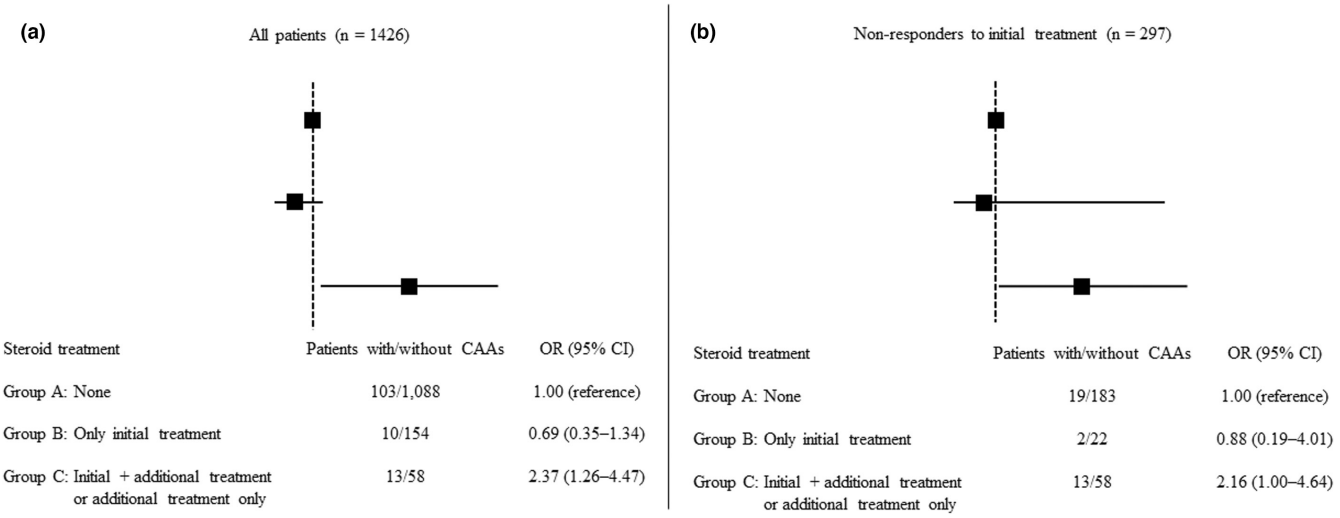


**FIGURE 4** Odds ratios and 95% confidence intervals of corticosteroid treatment for Kawasaki disease and coronary artery abnormalities. Corticosteroid combination treatment was divided into three groups (Group A = none, Group B = initial treatment only, and Group C = initial treatment + additional treatment or additional treatment only). Development of coronary artery abnormalities by the 30th day after Kawasaki disease onset was compared between these groups. (a) When Group A was used as a reference, the risk ratio was no different in Group B but was higher in Group C. (b) Limiting the target patients to those who did not respond to initial treatment (297 patients), the risk ratio was no different in Group B, but was higher in Group C. CAAs, coronary artery abnormalities; CI, confidence interval; OR, odds ratio.

## Relationship between treatment protocol and CAAs

Currently, corticosteroid therapy is most often combined with IVIG therapy. According to current guidelines, corticosteroids can be used at any stage of KD treatment.[8] To evaluate the effects of different timings of corticosteroid therapy on the coronary arteries, the corticosteroid combination treatment was divided into three groups (A = none, B = initial treatment only, and C = initial treatment + additional treatment or additional treatment only) and compared with the rate of development of CAA by the 30th day after KD onset. When Group A was used as a reference, the risk ratio was no

different in Group B; however, it was higher in Group C (Figure 4a). The same assessment was conducted on patients who had not responded to initial treatment (297 patients). Similar to the above results, when Group A was used as a reference, the risk ratio was no different in Group B but was higher in Group C (Figure 4).

## Examination of CAA predictors

We investigated the risk factors for KD in patients who had developed CAAs by the 30th day after KD onset. Univariate analysis performed using blood test results, age<1 year, sex, rate of non-responsiveness to initial treatment, and pre-*Z*-max ≥1.9 revealed that the highest ALT and TB concentrations, age <1 year and pre-*Z*-max ≥1.9 were predictors of CAAs (Table 3). When the four items that showed significant differences in univariate analysis and two items (sex and rate of non-responsiveness to initial treatment – also identified by our univariate analysis) previously identified as risk factors for CAAs were examined by multivariable analysis, age <1 year and pre-*Z*-max ≥1.9 were found to be independent predictors of CAAs (Table 4).

# DISCUSSION

In this study, we examined the data of 1426 patients from whom data were collected as part of the 24th Japanese Nationwide Survey on Kawasaki Disease in the Kinki area in 2016. This epidemiological study is the first to report the details of treatment administered to patients with KD in clinical practice. In this study, the frequency of CAAs increased from 3.0% to 8.8% when CAAs were defined using the *Z*-score criterion as opposed to the JMH criterion. We found age <1 year and pre-*Z*-max ≥1.9 to be useful predictors of CAA onset.

In line with the 2012 guidelines, 182 of 1426 (12.8%) patients with KD had been treated with corticosteroids as the initial treatment. For second-line treatment, corticosteroids were the most common additional treatment after IVIG alone, accounting for 50 of 297 (16.8%) of the total. Corticosteroids are used at many core hospitals that treat KD. Alternative treatments to corticosteroids were administered significantly more frequently as third-line treatment because each hospital has different treatment approaches and unique protocols.

The incidence of CAAs did not differ between patients who had undergone initial treatment with corticosteroids (Groups B and C) and those who had not received corticosteroids (Group A). In contrast, the RAISE study[3] showed that initial treatment with corticosteroids is effective in preventing development of CAAs. This discrepancy may be explained by the retrospective nature of the present study. In the additional investigation, which targeted only those who had not responded to initial treatment ($n$ = 297), the risk of CAAs was higher in the group that had received corticosteroids as an additional treatment (Group C). This may be because corticosteroids tend to be used in severe cases with high Gunma scores, which may be associated with an increased risk of CAAs. Conversely, corticosteroids often mask fever, which is important for determining their therapeutic effect. The number of days of illness increased in parallel with the risk of CAA. Although additional treatment should be started promptly in the absence of a response to initial treatment, additional treatment may be delayed

**TABLE 3** Results of univariate analysis of possible predictors of CAAs

| Variable | CAAs | No CAAs | *p* |
|---|---|---|---|
| Age <1 year | 48 (38.7) | 249 (19.2) | <0.0001 |
| Male sex | 65 (51.6) | 710 (54.6) | 0.5140 |
| Pre-*Z*-max of ≥1.9 | 77 (61.1) | 290 (22.3) | <0.0001 |
| WBCs, /μl | 15,465 (11,845–19,685) | 14,700 (12,100–18,753) | 0.2642 |
| Neut, % | 64.9 (50.1–76.8) | 68.0 (55.5–79.0) | 0.0568 |
| Neut, /μl | 9715 (6900–13,499) | 9821 (7154–13,455) | 0.7859 |
| Minimum Plt, /μl | 30.5 (24.1–36.5) | 30.6 (25.2–36.8) | 0.7104 |
| AST, IU/L | 59 (39–114) | 48 (37–93) | 0.0525 |
| ALT, IU/L | 56 (22–145) | 36 (17–110) | 0.0174 |
| TB, mg/dl | 0.6 (0.5–1.1) | 0.6 (0.4–0.9) | 0.0248 |
| Na, mEq/L | 134 (132–136) | 134 (132–136) | 0.2208 |
| CRP, mg/dl | 7.90 (4.74–11.79) | 7.38 (4.43–11.54) | 0.5394 |
| IVIG resistance | 34 (27.0) | 263 (20.2) | 0.0844 |

*Note*: Data are presented as median (interquartile range) or *n* (%). Comparisons were performed using the $\chi^2$ test for categorical variables or Mann–Whitney *U*-test for continuous variables.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CAAs, coronary artery abnormalities; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; Na, sodium; Neut, neutrophils; Plt, platelets; Pre-*Z*-max, maximum coronary artery *Z*-score for each coronary artery branch before treatment of Kawasaki disease; TB, total bilirubin; WBCs, white blood cells.

**TABLE 4** Multivariable logistic regression analysis of predictors of coronary artery abnormalities

| Variable | Odds ratio | 95% confidence interval | *p* |
|---|---|---|---|
| Age <1 year | 2.427 | 1.602–3.677 | <0.0001 |
| Male sex | 0.927 | 0.626–1.374 | 0.7061 |
| Pre-*Z*-max of ≥1.9 | 5.138 | 3.469–7.610 | <0.0001 |
| ALT, IU/L | 1.973 | 0.306–12.721 | 0.4850 |
| TB, mg/dl | 3.333 | 0.333–33.369 | 0.3247 |
| IVIG resistance | 1.495 | 0.953–2.345 | 0.0799 |

Abbreviations: ALT, alanine transaminase; IVIG, intravenous immunoglobulin; Pre-*Z*-max, maximum coronary artery *Z*-score for each coronary artery branch before treatment of Kawasaki disease; TB, total bilirubin.

in clinical practice because of the transient antipyretic effect of corticosteroids. Our study cohort was too small to compare the results of additional treatments other than corticosteroids. Thus a multicenter study is needed in the future.

The second consideration is the differences in frequency of diagnosis of CAAs with different diagnostic criteria. The JMH definition may underestimate the frequency of CAAs compared with the new definition based on the *Z*-score.[18] In this study, we investigated the frequency of CAAs diagnosed on the basis of the *Z*-score, which is not yet commonly used in Japan. We found that the frequency of CAAs increased from 3.0% to 8.8%. Thus, when the new definition based on the *Z*-score is applied, the frequency of diagnosis of CAAs is expected to increase. The criteria for diagnosing CAAs have not yet been standardized, different criteria being used in different hospitals. Thus, it is possible that the frequency of CAAs was underestimated by this nationwide survey. Clinicians should be aware that the rate of diagnosis of CAA varies according to the criteria used to diagnose these abnormalities. It is therefore necessary to explore whether all patients with *Z*-scores ≥2.5 at 4 weeks after the onset of KD should be followed up as having CAAs.

In this study, most CAAs that were not defined by the JMH definition were mild and were classified as small aneurysms. Even when CAAs are small and regress rapidly, inflammatory changes persist in their region for long periods.[19] Thus, *Z*-scores should be calculated to avoid overlooking small CAAs.

The third consideration is the predictors of development of CAA, which include sex (male), age (infants and older children), and failure to respond to initial IVIG.[20–22] It has recently been reported that an increase in the coronary artery *Z*-score before initial IVIG treatment (pre-*Z*-max) is a risk factor for CAAs.[15–17] Pre-*Z*-max can be used to evaluate the coronary arteries directly and may be one of the predictors of CAAs. However, because the frequency of CAAs may change depending on the varying additional treatments in a single-center study, the reported cutoff values for pre-*Z*-max as a predictor have ranged from 1.4 to 2.0.[15–17] No standard cutoff value has yet been established.

In this study, we performed a univariate analysis using selected blood test findings, age <1 year, sex, nonresponse rate, and pre-*Z*-max, which are reported predictors of CAAs. We found significant differences in maximum ALT and TB concentrations, age <1 year and pre-*Z*-max. Subsequent multivariable analysis identified age <1 year and pre-*Z*-max as independent risk factors for CAAs. The finding that age <1 year is a risk factor for CAA is consistent with previous studies.[23–25]

Autopsy examinations have shown that changes in the coronary artery wall begin with inflammatory cell infiltration on the sixth to eighth days, whereas dilation begins from the 12th day.[26] Dilation of the coronary artery wall can likely occur earlier than the sixth to eighth days. Autopsy findings suggest that such dilation is a predictor of CAAs.[26] Another consideration is that the coronary artery wall has three-layers, comprising the intima, media, and adventitia. It is thought that CAAs develop when the media has been destroyed (ruptured) by inflammation.[19] These reports and our results suggest that it may be important to prevent damage to, and dilatation of, the coronary arteries from the early acute phase of KD. It is therefore necessary to determine what the optimal first line protocol is in patients with KD and a high pre-*Z*-max.[15–17]

## Limitations

This study has some limitations that should be noted. First, there were some differences between the analysis and missing data groups and the missing data group was large. We consider that the low response rate was attributable to the fact that the secondary questionnaire was very long; thus, most of the hospitals that responded were relatively large. Second, this study was based on a retrospective secondary questionnaire survey. However, it reveals the actual status of KD treatment in clinical practice and helps in selecting optimal treatment for KD. Third, because this was not a randomized controlled trial the level of evidence concerning treatment outcomes was low. Although we could not link additional treatment directly with CAA outcomes, we were able to clarify the optimal second- and third-line treatments for non-responders and *Z*-scores for CAA outcomes in the Kinki area in 2016. Fourth, it is difficult to measure the coronary artery diameter and height accurately. Moreover, many patients with KD are infants, and measurements of coronary artery diameters by pediatricians are not necessarily consistent, leading to variability in the *Z*-score.

## CONCLUSION

The treatment guidelines for acute KD were updated in 2012. We researched the status of acute treatment, distribution of coronary artery diameters, and blood test results of patients with KD in the Kinki area in 2016. We also investigated the predictors of development of CAA. The frequency of CAAs was significantly greater when the *Z*-score criterion was used. Treatment up to second-line treatment was almost standardized, whereas third-line treatment varied between hospitals. Using corticosteroids as an additional treatment should be carefully monitored. Age<1 year and pre-*Z*-max of ≥1.9 were found to be useful predictors of development of CAA. New methods for evaluating coronary arteries and new treatments for KD are expected to be discovered in the future. It is important to investigate the effects of treatment at regular intervals in clinical practice.

### AUTHOR CONTRIBUTIONS

Hiroyuki Suzuki, Kazuyuki Ikeda, Masafumi Izui, Naho Kobayashi, Ken Yoshimura, Naho Kobayashi, and Nobuyuki Kakimoto conceived and designed the study. Nobuyuki Kakimoto, Kazuyuki Ikeda, Masafumi Izui, Naho Kobayashi, Ken Yoshimura, and Tomohiro Suenaga were involved in data collection. Nobuyuki Kakimoto, Tomoya Tsuchihashi, and Naomi Kitano constructed the database. Tomoya Tsuchihashi performed the statistical analyses and drafted the first version of the article. Hiroyuki Suzuk was the principal investigator and managed the study progress, promoted data collection, coordinated the study, supervised the results of analysis, interpreted the findings, and critically reviewed and revised the article. Naomi Kitano obtained funding, provided administrative support, supervised the analyses, and reviewed and revised the article. Tomohiro Suenaga coordinated the study and critically reviewed the article for important intellectual content. Yoshikazu Nakamura provided an extracted dataset from the nationwide study, supervised the study, and critically reviewed the article for important intellectual content. All the authors approved the final article and agreed to submit the article for publication.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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