Delayed Development of Coronary Artery Aneurysm in Patients with Kawasaki Disease Who Were Clinically Responsive to Immunoglobulin

Ryohei Matsuoka, MD[1,4], Kenji Furuno, MD, PhD[1,2], Etsuro Nanishi, MD, PhD[4], Sagano Onoyama, MD[2], Hazumu Nagata, MD, PhD[4], Kenichiro Yamamura, MD, PhD, MSc (Epidemiology)[4], Yuichiro Sugitani, MD[3], Ayako Kuraoka, MD[3], Yumi Mizuno, MD, PhD[2], Koichi Sagawa, MD[3], Satoshi Honjo, MD, PhD, MSc (Epidemiology)[5], Toshiro Hara, MD, PhD[2], and Shouichi Ohga, MD, PhD[4]

Objective To clarify the frequency and characteristics of discrepant outcomes of intravenous immunoglobulin (IVIG) between fever and coronary artery aneurysms (CAAs) in patients with Kawasaki disease.

Study design This study included 325 patients who responded to oral aspirin and IVIG alone. The main outcome was CAA 4 weeks after disease onset. CAA was defined as ≥2.5 of maximum z score (Zmax) representing the highest value of 4 coronary artery branches. Immunoglobulin dosage and sequential changes in Zmax were reviewed to investigate the effects on fever and timing of CAA development. Logistic regression analyses with receiver operating characteristic curves using clinical and laboratory variables including the initial Zmax were performed to identify predictors of CAA at 4 weeks.

Results CAAs were either persistent or appeared de novo 4 weeks after diagnosis in 13 of 325 patients who responded to a single or repeated IVIG. Four single-dose IVIG-responders developed CAA although they had pretreatment Zmax of <2.0. The 2 single-dose IVIG responders with the greatest pretreatment Zmax (>4.5) developed persistent CAA. Receiver operating characteristic analysis demonstrated Zmax of 2.57 as the cut-off for predicting CAA. Multivariable analyses identified >2.5 Zmax (OR 9.08, 95% CI 1.26-65.3, P = .028, 50% sensitivity, 91% specificity) as the sole risk factor for CAA at 4 weeks in single-dose IVIG responders.

Conclusions Delayed development and persistence of CAA in single-dose IVIG responders indicate that some factors other than those responsible for systemic inflammation may contribute to vasculitis in CAA. Baseline Zmax 2.5 aids in predicting CAAs. *(J Pediatr 2020;227:224-30)*.

Kawasaki disease is an acute, febrile vasculitis syndrome that preferentially affects coronary arteries.[1-3] Recent advances in the treatment of Kawasaki disease have greatly reduced the incidence of coronary artery aneurysm (CAA). Nevertheless, Kawasaki disease remains the commonest cause of acquired heart disease in childhood in developed countries. High-dose intravenous immunoglobulin (IVIG) within the first 10 days of illness reduces the risk of developing CAA from 25% to <5%[4]; patients with persistent fever after receiving IVIG are at high risk of developing CAAs. However, patients occasionally develop CAAs after defervescence with prompt IVIG treatment. The frequency of and explanation for this discrepancy between the effects of IVIG on fever and coronary arteries remain unclear. Several scoring systems involving combinations of inflammatory markers may predict the response of fever to IVIG treatment but do not reliably predict the risk of developing CAA.[5]

Standard z scores for coronary artery diameter assessed by echocardiography have been widely used in clinical settings.[6] Use of this scoring system, in which each coronary artery diameter is adjusted for body size, facilitates accurate real-time monitoring of CAA without coronary angiography.[3] Several studies have reported that initial coronary artery dilatation is associated with development of CAA.[7-10] Using multivariable logistic analysis, Liu et al[7] showed that ≥2.5 of an initial maximal coronary z score (maximum Z score [Zmax]; OR, 5.24; CI 1.31-21.3; P = .020) and <3.5 g/dL of hypoalbuminemia (OR 4.83; CI 1.11-20.9; P = .035) are independently associated with development of CAA. Son et al[8] reported that ≥2.0 of initial Zmax predicts development of CAA with 80% sensitivity and 98% negative predictive value. The baseline Zmax is thus considered a more useful marker of CAA than other biomarkers. However, the ideal cut-off values for predicting development of CAA have not been determined.

To clarify the effects of IVIG on fever and CAA in Kawasaki disease, we monitored z scores in a specific cohort of single or repeated IVIG responders over

CAA	Coronary artery aneurysm
IVIG	Intravenous immunoglobulin
ROC	Receiver operating characteristic
Zmax	Maximum z score

From the [1]Department of General Pediatrics and Interdisciplinary Medicine; [2]Kawasaki Disease Center; and [3]Department of Pediatric Cardiology, Fukuoka Children's Hospital; [4]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University; and [5]Department of Pediatrics, National Hospital Organization Fukuoka National Hospital, Fukuoka, Japan

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24 months. We investigated the discrepancy between defervescence and coronary outcomes in terms of the process of systemic and vascular inflammation. We also evaluated the clinical utility of initial Zmax and other clinical and laboratory variables for predicting coronary outcomes.

Methods

Data on patients in the Kawasaki disease center registry of Fukuoka Children's Hospital who had been diagnosed with complete Kawasaki disease and treated for it between November 1, 2014, and March 31, 2017, were examined in the present study. Diagnoses of Kawasaki disease were made in accordance with the Japanese diagnostic guideline for Kawasaki disease.[11] Patients with incomplete Kawasaki disease were not included. In our institutional treatment protocol, all patients had received initial treatment of a single or repeated infusion(s) of 2 g/kg IVIG and a conventional dose of aspirin (30-50 mg/kg/d), as specified in the Japanese guideline.[12] If the Kobayashi score was ≥5 at the time of diagnosis of Kawasaki disease, we proposed to the patient's family an option to add corticosteroids as initial treatment, and used it if consent was obtained. Failure to respond to IVIG was defined as persistent or recurrent fever (≥37.5°C) at 36 hours after completion of each infusion.[13] Rescue treatments were administered to a patient who did not respond to second IVIG, including infliximab, and corticosteroid along with plasma exchange until complete defervescence. The inclusion criteria for this retrospective case–control study were patients with Kawasaki disease who responded to single or repeated doses of IVIG and did not receive other rescue treatments. The exclusion criteria were patients who had underlying congenital heart disease; had been transferred from other hospitals after treatment of Kawasaki disease; had their coronary arteries inaccurately measured; had received the diagnosis over 10 days after the onset of fever; and were not responsive to single or multiple dose(s) of IVIG, and received other anti-inflammatory agent(s) as rescue therapy. No patients had a previous history of Kawasaki disease.

Medical records were reviewed to collect clinical, laboratory, and echocardiographic data along with details of treatments and outcomes. Kobayashi scores were calculated for each patient, these reportedly being predictors of unresponsiveness to initial IVIG therapy among Japanese children.[5] Because this was a retrospective observational study, the requirement for informed consent was waived. This study was approved by the institutional review board at Fukuoka Children's Hospital (approval number, 29-51).

The diameters of the right, left main, left anterior descending, and left circumflex coronary arteries were measured in all patients by echocardiography using the standard measurement methods recommended by the Japanese Society for Kawasaki Disease.[14] The results were reviewed by 2 experienced pediatric cardiologists for each patient. The initial echocardiography was performed on the day of diagnosis and every few days until 1 week after defervescence, after which echocardiography was performed at least every 2 weeks until 4-6 weeks after treatment. Echocardiography was performed more frequently in patients who developed CAA than in those who did not until the CAA regressed. The coronary artery diameters were converted to z scores after adjusting for the body surface area in accordance with a standard method established for Japanese children.[6] Zmax was defined as the largest z score in the 4 branches at the time of measurement. CAA was defined as having ≥2.5 of the Zmax. The primary outcome of this study was CAA status 4 weeks after the onset of Kawasaki disease.

The IVIG dosage and timing of development of CAA in the patients with Kawasaki disease who had CAA at 4 weeks were analyzed. Clinical and laboratory data were then compared between the patients with and without CAA at 4 weeks using the independent sample t test, Mann–Whitney U test, and Pearson χ^2 test. Log-transformed values were used in the statistical analyses when the original values were not normally distributed. Intra- and interobserver agreement of Zmax on 30 randomly selected subjects were evaluated by intraclass correlation coefficient. Receiver operating characteristic (ROC) curves were generated to identify the cut-off value of pretreatment Zmax (baseline score at diagnosis) for development of CAA during and after treatment. Youden J statistics were used to determine the cut-off value.[15] Logistic regression analysis was then performed to obtain a crude OR of clinical and laboratory variables for the development of CAA. Multivariable logistic regression analysis to identify determinants for development of CAA or IVIG unresponsiveness or diagnosis of Kawasaki disease were always adjusted for the dichotomized z score (cut-off value or greater vs less than the cut-off value) and age at onset, sex, number of days with fever (≥37.5°C) before treatment of Kawasaki disease, white blood cell count, platelet count, aspartate aminotransferase, brain natriuretic peptide, albumin, C-reactive protein, and total bilirubin, these factors having been identified in previous studies.[5,16-19]

Two-sided P values of <.05 were considered to indicate statistical significance. The Bonferroni correction was applied for multiple comparisons. Statistical analyses were performed with the EZR software program,[20] version 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 405 patients were diagnosed with complete Kawasaki disease. After the exclusion of 80 patients in accordance with the exclusion criteria, 325 patients were enrolled in this study (**Figure 1**; available at www.jpeds.com), 13 (3.9%) of whom had CAA 4 weeks after the onset of Kawasaki disease. No patient was newly diagnosed with CAA after the 4-week time point. Patient characteristics, laboratory data at diagnosis, and treatments were compared between patients with and without CAA 4 weeks after

disease onset (Table I). The median age at diagnosis of Kawasaki disease was significantly younger in patients with CAA than in those without it (median 11 vs 25 months, $P = .008$). The total duration of fever was significantly longer in patients with CAA than in those without it (6 vs 5 days, $P = .045$). Brain natriuretic peptide concentrations at diagnosis were significantly greater in the CAA than the non-CAA group (50 vs 21 pg/mL, $P = .005$), as was the pretreatment Zmax (3.26 vs 1.57, $P < .001$). Of 325 patients, 247 (76%) responded to a single-infusion of IVIG, and 78 (24%) responded to repeated infusions (65 receiving a second, 12 a third, and 1 a fourth infusion). In our hospital, we usually select infliximab or plasma exchange as third-line therapies in most cases. However, these 13 patients received third and fourth IVIG, because they had fever again after they had initially responded to a second IVIG dose; they developed Kawasaki disease before December 2015, when infliximab was approved in Japan; or consent for administration of infliximab or plasma exchange could not be obtained. Patients achieved defervescence by a median of day 5 after fever onset (range from day 2 to 25). No patients died or dropped out of the study during the study period. There was no significant difference in the other clinical variables between the study groups.

Intra- and interobserver agreement of Zmax by intraclass correlation coefficient was 0.95 and 0.97, respectively. ROC analysis was performed to determine the coronary artery Zmax that might predict post-treatment CAA. The cut-off value of Zmax assessed by Youden J statistics[15] was 2.57, with sensitivity of 69% and specificity of 92%. The positive predictive value was 27% and the negative predictive value was 99%. ROC analysis yielded an area under the curve of 0.82 (95% CI 0.67-0.97). Specificity was greater for >2.5 than >2.0 of baseline Zmax in all 325 patients (Table II [available at www.jpeds.com], 0.90 vs 0.74) and 247 initial IVIG-responders (Table III [available at www.jpeds.com], 0.91 vs 0.75); however, sensitivity did not differ between these 2 values in both all 325 patients (0.69 vs 0.69) and 247 initial IVIG-responders (0.50 vs 0.50).

Clinical characteristics at diagnosis and changes in Zmax of the 13 patients with CAA are shown in Table IV. All CAAs had Z scores ranging from ≥2.5 to <5 and were classified as small aneurysms in accordance with the definition in the statement of the American Heart Association.[3] Eight of them (62%) had responded to a single infusion of IVIG. When possible, predictors of CAA were investigated in all 325 patients with Kawasaki disease and the subgroup of 247 single-dose IVIG-responders (Tables V and VI; available at www.jpeds.com), pretreatment Zmax was identified as the sole significant variable that distinguished those who would develop CAA from those who would not at the time of diagnosis. Four of the 13 (31%) patients with CAA had pretreatment Zmax of <2.5 (patients 2, 5, 8, 9, Table IV, Figure 2). All 4 patients had non-severe Kobayashi scores, and defervescence before day 7 of illness after a single infusion of IVIG. Nine of the 13 patients had blood tests performed 4 weeks after the onset, and their CRP levels and white blood cell counts were within the normal range. CAAs

Table I. Demographics, baseline characteristics, and treatment of patients with or without CAA

Characteristics	CAA at 4 weeks, n = 13	No CAA at 4 weeks, n = 312	P*
Age at onset,† mo	11 (3-74)	25 (0‡-185)	.008
Age ≥12 mo, n	5 (38)	243 (77.9)	.003
Female sex, n	5 (38)	141 (45.1)	.78
Febrile days until the diagnosis, d	5 (3-9)	5 (2-9)	.68
Duration of total fever, d	6 (3-18)	5 (2-25)	.045
Kobayashi score, points	3 (1-8)	3 (0-10)	.54
Laboratory data at diagnosis			
White blood cell, $\times 10^9$/L	14 (5.9-22)	14 (2.9-31)	.97
Neutrophil, $\times 10^9$/L	7.7 (3.8-18)	9.5 (0.82-29)	.23
Lymphocyte, $\times 10^9$/L	4.2 (0.50-10)	3.0 (0.52-13)	.14
Neutrophil/lymphocyte ratio†	1.9 (0.92-10)	3.2 (0.15-53)	.12
Hgb, g/dL	11 (8.5-13)	11 (8.1-15)	.24
Platelet, $\times 10^9$/L	344 (111-1182)	362 (99-746)	.87
Albumin, g/dL	3.8 (2.6-4.4)	3.8 (2.1-5.1)	.85
BNP,† pg/mL	50 (9.2-1870)	21 (5.8-614)	.005
Aspartate aminotransferase,† IU/L	37 (19-130)	33 (2.0-1956)	.78
Alanine aminotransferase,† IU/L	19 (10-116)	20 (5.0-961)	.59
Total bilirubin, mg/dL	0.4 (0.2-2.0)	0.6 (0.1-4.9)	.096
Sodium, mEq/L	135 (133-140)	136 (128-142)	.52
C-reactive protein,† mg/dL	9.8 (2.0-18)	7.3 (0.42-31)	.38
Pretreatment z score			
Maximum	3.26 (0.96-4.79)	1.57 (−1.03 to 4.36)	<.001
≥2.5 of maximum z score, n	9 (69)	31 (9.9)	<.001
Treatment			
Total dose of IVIG, g/kg	2 (2-7)	2 (2-6)	.14

BNP, brain natriuretic peptide.
Values are expressed as n (%) or median (range).
CAAs were defined as >2.5 of Zmax score at 4 wk after the onset of Kawasaki disease.
*Independent sample t test and Mann–Whitney U test for median for continuous values; Pearson χ^2 test for qualitative values.
†Log-transformed values were used.
‡The youngest patient presented 4 weeks after birth.

Table IV. Clinical characteristics and clinical course of patients with CAA

		At diagnosis of Kawasaki disease								At diagnosis of CAA				
No.	Sex	Age, mo	Days after onset	WBC, $\times 10^9$/L	CRP, mg/dL	T-Bil, mg/dL	BNP, pg/mL	Kobayashi score	Baseline Zmax	Number of days with fever	Days after onset	BT, °C	Zmax at 4 wk	Period for normalization, mo	IVIG, g/kg
1	M	11	3	22.0	7.7	0.6	98.3	4	3.48	3	3	38.3	3.27	2	2
2	M	24	5	11.7	18.2	0.4	270.5	3	1.37	6	12	36.8	2.85	2	2
3	M	74	4	5.9	10.7	0.7	NA	8	2.57	6	4	38.1	2.60	2	4
4	F	10	6	21.6	9.8	0.3	1870.2	5	3.36	18	6	39.2	3.04	2	7
5	F	16	3	6.4	12.2	0.4	21.8	4	1.35	3	7	36.8	2.58	2	2
6	M	11	8	14.2	10.3	0.7	29.1	1	3.77	10	8	38.4	2.62	4	4
7	F	9	9	12.5	2.7	0.2	9.2	2	2.73	9	10	36.6	3.00	4	2
8	M	12	4	12.0	12.9	2.0	50.0	3	1.99	5	10	37.2	3.55	6	2
9	M	10	7	16.4	2.1	0.2	10.7	3	0.96	7	16	36.2	3.98	8	2
10	F	13	4	17.8	2.0	0.5	14.8	2	4.13	15	4	37.5	3.86	12	4
11	M	3	5	12.8	12.0	0.8	73.1	5	3.26	10	7	39.0	3.12	18	6
12	M	7	3	21.8	5.3	0.4	NA	1	4.79	3	4	37.6	4.06	>36*	2
13	F	6	6	17.3	7.9	0.3	643.7	1	4.55	6	6	39.9	2.61	>36*	2

BT, body temperature, *CRP*, C-reactive protein; *F*, female; *M*, male; *NA*, not applicable; *T-Bil*, total bilirubin; *WBC*, white blood cel; *BNP*, brain natriuretic peptide.
CAAs were defined as ≥2.5 of Zmax score at 4 weeks after the onset of Kawasaki disease.
*Patients 12 and 13 continued to have CAA with 3.0 of Zmax measured by echocardiography over 36 months after the onset of Kawasaki disease.

persisted for over 2 years only in 2 infants who were single-dose responders with pretreatment Zmax of >4.5 (patients 12, 13, Table IV and Figure 2). There was no difference in the duration of fever before diagnosis between the 9 patients with CAA at diagnosis of Kawasaki disease, 4 who developed CAA later, and 312 who did not develop CAAs according to covariance analysis (Figure 3). No variables at diagnosis differed significantly between patients with late development of CAA (n = 4) and all other groups of patients (Table VII; available at www.jpeds.com).

Discussion

The present study demonstrated that 4% of the responders to single- or multiple-dose(s) of IVIG had CAA 4 weeks after the onset of Kawasaki disease. We also found that Zmax at the time of diagnosis of Kawasaki disease was the only investigated variable that predicted development of CAA at 4 weeks with low sensitivity but high specificity. The low sensitivity is attributable to the fact that 4 (31%) of the 13 patients with CAAs had <2.0 Zmax at diagnosis (patients 2, 5, 8, 9; Table IV and Figure 2). Three of the 4 patients had high CRP levels (>10 mg/dL) and one had a diagnosis of 7 days (>5 days). However, all 4 had non-severe Kobayashi scores and had defervescence before day 7 of illness after a single infusion of IVIG. Contrary to our expectations, only 5 (38%) of the patients with CAAs were initial IVIG failures. Moreover, long-lasting CAAs developed only in 2 infants who were both single-dose responders. These results suggest that, in patients with Kawasaki disease, different pathologies could be responsible for IVIG resistance and CAA-formation.

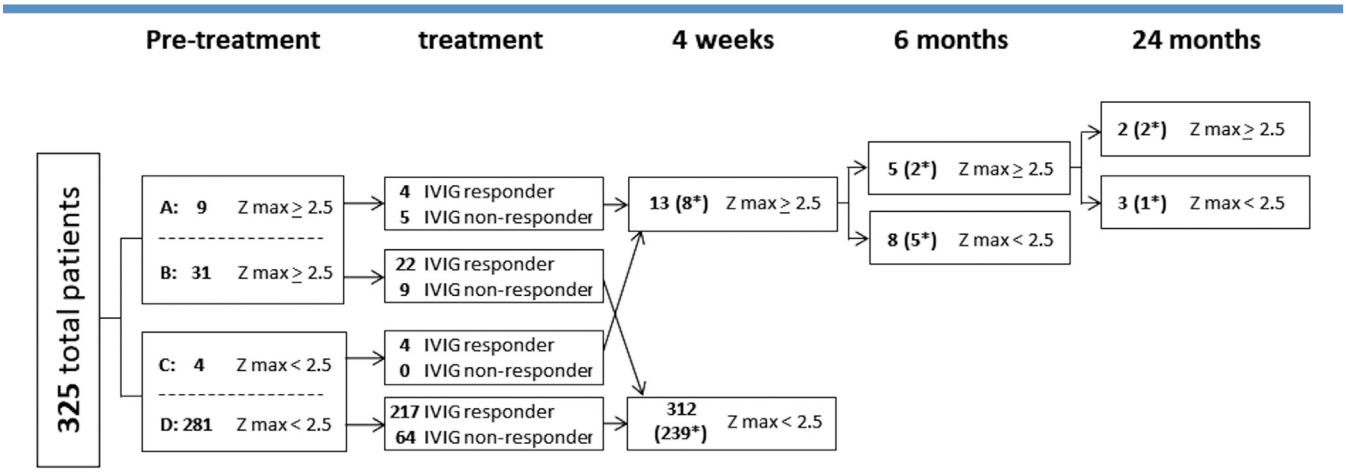

Figure 2. Follow-up Zmax and treatment responses of a single or repeated IVIG responders during 24 months after the onset of Kawasaki disease. The patients were divided into the following 4 groups according to the coronary artery aneurysm development and its timing in the clinical course. *The number of initial single-dose IVIG responders.

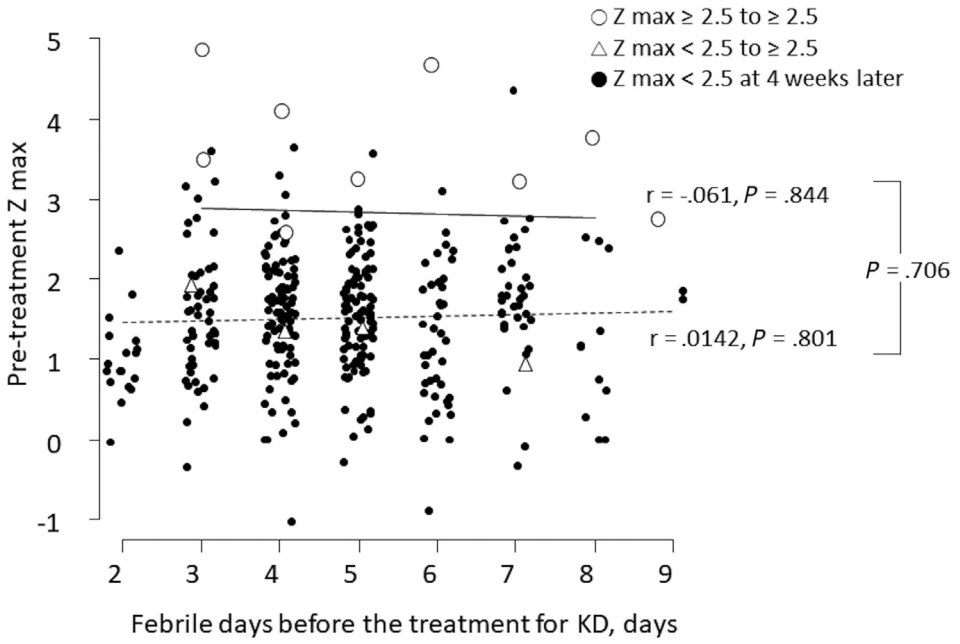

Figure 3. The correlation between febrile days and pretreatment Zmax. *Open circles* indicate patients with Zmax from pre-treatment ≥2.5 to post-treatment ≥2.5. *Open triangles* indicate patients with Zmax from pretreatment <2.5 to post-treatment ≥2.5. *Closed circles* indicate patients without CAA. *Solid line* (CAA) and *dotted line* (no CAA) represent the regression lines. *KD*, Kawasaki disease; *r*, correlation coefficient.

The principle of Kawasaki disease treatment is to diminish inflammation as rapidly as possible by administering IVIG with the aim of preventing development of CAA.[10,21,22] Persistence of CAAs beyond 4 weeks after diagnosis of Kawasaki disease is the critical factor leading to myocardial ischemia because of coronary artery stenosis and thrombosis. Even transient CAA that regressed during treatment may cause coronary artery endothelial dysfunction in adolescence and adulthood.[23] Therefore, early identification of patients at high risk of developing CAA and administration of more intensive treatment to those patients is important. In Japan, several stratification scoring systems for identifying high-risk patients have been proposed[5,16,17,24]; however, the practical usefulness of these scores remains controversial in other countries.[25-27] Of interest, recent studies on patients of various ethnicities have reported that coronary artery dilatation at diagnosis is associated with development of CAA.[7-10] The cut-off values for Zmax at diagnosis ranged from 2.0 to 3.0 in these studies. In our analysis of IVIG responders, the ROC curve identified 2.57 as the cut-off value of Zmax. A baseline Zmax >2.5 predicted development of CAA with greater specificity than baseline Zmax >2.0. A pretreatment Zmax of 2.5 is therefore the optimal cut-off value for risk stratification before treatment of Kawasaki disease.

In the present study, 31 of 40 patients (Group B in **Figure 2**) with pretreatment Zmax ≥2.5, which is beyond the degree of physiological dilation due to fever,[28,29] showed rapid resolution by the time of 4 weeks (**Figure 3**). This result indicated that coronary arteritis does not seem to be confined to those patients who show persistent dilatation or aneurysms at 4 weeks. However, many of these patients had a decrease in the vasculitic process within 4 weeks under the standard treatment with IVIG and aspirin. On the other hand, 4 out of 13 patients (patients 2, 5, 8, 9; **Table IV** and **Figure 2**) who developed CAA at 4 weeks initially had Zmax <2.5 at the diagnosis of Kawasaki disease. Two patients with persistent CAA with the largest and second largest Zmax were infants (patients 12, 13; **Table IV** and **Figure 2**). Salgado et al[30] reported that 19% of the young infants had normal echocardiograms at diagnosis of Kawasaki disease but CAA on subsequent echocardiograms within 8 weeks of diagnosis. Although it is unclear whether patients who had coronary dilation were IVIG responders, this fact is partially consistent with our study results. Restricting eligibility for the present study to single or repeated IVIG responders allowed us to clarify the fact that even IVIG responders may develop CAA after defervescence.

In patients with severe Kawasaki disease, the effectiveness of adjunctive therapies for primary treatment using short-term corticosteroid, infliximab, or calcineurin inhibitors has been reported. If a patient has a Zmax ≥2.5 at diagnosis of Kawasaki disease, it may be beneficial to consider intensification of the first-line therapy. However, the optimal therapy has not been established, and even these proactive anti-inflammatory treatments do not completely prevent the development of CAA.[31-36] Adding glucocorticoids to IVIG reportedly decreases the probability of developing CAA in Japanese children identified as being at high risk by stratification scores using multiple clinical variables.[16,31]

However, these studies excluded patients who had CAA before treatment. It is unclear whether adjunctive glucocorticoids limit progression of CAA that are present at the time of diagnosis of Kawasaki disease. Our study group has recently reported that infliximab therapy is associated with early regression of moderate CAA (Zmax >3.5) but does not reduce the final proportion of patients with CAA.[34] Based on these reports and the present findings, the mechanisms of developing CAA may not be explained by systemic inflammation alone. Intensified anti-inflammatory therapy is expected to minimize CAA formation; however, clonal and epigenetic events may contribute to the subsequent vascular remodeling that results in regression of CAA.[37] Genome-wide association and linkage studies have identified genes associated with susceptibility to Kawasaki disease, including *ITPKC*, *CASP3*, *CD40*, and *ORAI1*,[38] in addition to environmental factors.[39,40] Both the intensity of anti-inflammatory treatment according to the Zmax[4] and vasculitis-associated genes may predispose high-risk patients to vascular inflammation and subsequent CAA.

The present study had several limitations that warrant mention. First, the study was retrospective, and the exclusion of patients transferred to our institution resulted in a relatively small study cohort. Second, the times of administration of repeated IVIG may have been biased according to the general condition of the patient. Further large, prospective, confirmatory studies are warranted. Genetic and epigenetic factors affecting defervescence and progression of CAA may need to be considered when establishing stratified treatment for Kawasaki disease. ■

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Reprint requests: Kenji Furuno, MD, PhD, Department of General Pediatrics and Interdisciplinary Medicine, Fukuoka Children's Hospital, 5-1-1, Kashii-Teriha, Higashi-ku, Fukuoka City, Fukuoka 813-0017, Japan. E-mail: furuno.k@fcho.jp

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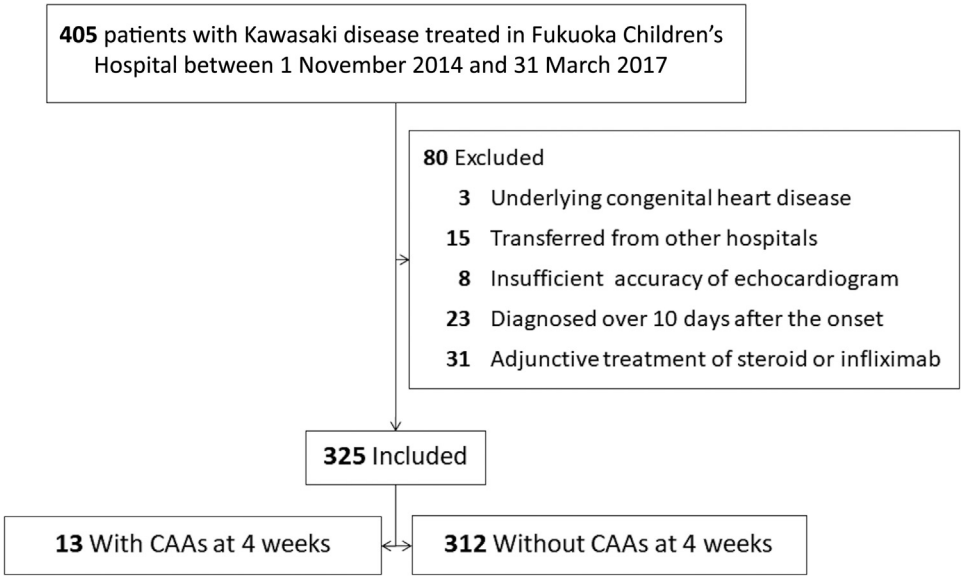

Figure 1. Flowchart of 325 patients with Kawasaki disease who responded to a single or repeated infusion(s) of IVIG. Thirteen patients developed coronary artery aneurysms 4 weeks after the onset of Kawasaki disease.

Table II. Two cut-off values of baseline Zmax that predict the development of CAA in all 325 patients

Cut-off points of Zmax at diagnosis	>2.5, n = 40	>2.0, n = 90	*P**
Sensitivity	0.69 (0.39-0.91)	0.69 (0.39-0.91)	
Specificity	0.90 (0.86-0.93)	0.74 (0.69-0.79)	
Positive predictive value	0.23 (0.11-0.39)	0.10 (0.05-0.18)	
Negative predictive value	0.99 (0.97-0.99)	0.98 (0.96-0.99)	
Diagnostic accuracy	0.89 (0.86-0.93)	0.74 (0.69-0.79)	
Positive likelihood ratio	7.0 (4.3-11.4)	2.0 (1.0-4.2)	
Negative likelihood ratio	0.34 (0.15-0.77)	0.41 (0.18-0.94)	
AUC of ROC	0.80 (0.67-0.93)	0.72 (0.59-0.85)	<.001

AUC, area under the curve.
Values are expressed as estimated value (95% CI).
CAAs were defined as ≥2.5 of Zmax at 4 wk after the onset of Kawasaki disease.
*DeLong test for 2 correlated ROC curves.

Table III. Two cut-off values of pretreatment Zmax that predict the development of CAA in 247 initial IVIG responders

Cut-off points of Zmax at diagnosis	>2.5, n = 26	>2.0, n = 64	P*
Sensitivity	0.50 (0.16-0.84)	0.50 (0.16-0.84)	
Specificity	0.91 (0.87-0.94)	0.75 (0.69-0.80)	
Positive predictive value	0.15 (0.04-0.35)	0.06 (0.02-0.15)	
Negative predictive value	0.98 (0.96-0.99)	0.98 (0.95-0.99)	
Diagnostic accuracy	0.90 (0.85-0.93)	0.74 (0.68-0.80)	
Positive likelihood ratio	5.5 (2.4-12.3)	2.0 (1.0-4.2)	
Negative likelihood ratio	0.55 (0.28-1.10)	0.67 (0.33-1.3)	
AUC of ROC	0.70 (0.52-0.89)	0.62 (0.44-0.81)	<.001

Values are expressed as estimated value (95% CI).
CAAs were defined as ≥2.5 of Zmax at 4 wk after the onset of Kawasaki disease.
*DeLong test for 2 correlated ROC curves.

Table V. Clinical variables in association with the risk for the development of CAA in 325 all patients

	n (%)		Univariate		Multivariate	
Variables	CAA at 4 wk, n = 13	No CAA at 4 wk, n = 312	Crude OR (95% CI)	P	a OR (95% CI)	P
Pretreatment Zmax ≥2.5	9 (69)	31 (9.9)	20.4 (5.93-70.1)	<.001	19.0 (4.01-90.4)	<.001
Age at onset ≥12 mo	5 (39)	243 (77.9)	0.18 (0.06-0.56)	.003	0.22 (0.04-1.08)	.062
Female sex	5 (39)	141 (45.2)	0.76 (0.24-2.37)	.63	1.34 (0.32-5.75)	.69
Febrile days until the diagnosis ≥5	7 (54)	174 (55.8)	0.93 (0.30-2.82)	.89	1.28 (0.26-6.39)	.76
White blood cell, $\geq 1.2 \times 10^9$/L	9 (69)	226 (72.4)	0.86 (0.26-2.85)	.80	0.54 (0.09-3.11)	.49
Platelets, $\geq 300 \times 10^9$/L	9 (69)	227 (72.8)	0.84 (0.25-2.81)	.78	0.41 (0.07-2.46)	.33
Albumin, ≥3.5 g/dL	9 (69)	258 (82.7)	0.47 (0.14-1.59)	.22	0.72 (0.13-4.09)	.71
AST, ≥100 IU/L	1 (8)	39 (12.5)	0.58 (0.07-4.61)	.61	1.95 (0.14-26.9)	.62
Total bilirubin ≥1.0 mg/dL	1 (8)	50 (16.0)	0.44 (0.06-3.43)	.43	0.48 (0.03-6.94)	.59
CRP, ≥10 mg/dL	6 (46)	84 (26.9)	2.33 (0.76-7.12)	.14	4.62 (0.91-23.5)	.065
BNP, ≥40 pg/mL	6 (55)	69 (29.9)	2.82 (0.83-9.54)	.096	1.68 (0.34-8.32)	.53

AST, aspartate aminotransferase.
OR for the continuous variables are interpreted as change in odds per every 1-unit increment for continuous variable.
CAA were defined as ≥2.5 of Zmax at 4 weeks after the onset of Kawasaki disease.

Table VI. Clinical variables in association with the risk for the development of CAA in 247 initial IVIG responders

Variables	n (%)		Univariate		Multivariate	
	CAA at 4 weeks, n = 8	No CAA at 4 weeks, n = 239	Crude OR (95% CI)	*P*	a OR (95% CI)	*P*
Pretreatment Zmax ≥2.5	4 (50)	22 (9.2)	9.86 (2.31-42.2)	.002	9.08 (1.26-65.3)	.028
Age at onset ≥12 mo	5 (38)	186 (77.8)	0.17 (0.04-0.74)	.018	0.18 (0.02-1.45)	.11
Female sex	3 (38)	112 (46.9)	0.68 (0.16-2.91)	.60	1.06 (0.19-5.92)	.95
Febrile days until the diagnosis ≥5	4 (50)	135 (56.5)	0.77 (0.19-3.15)	.72	1.19 (0.17-8.50)	.86
White blood cells, ≥1.2 × 10^9/L	5 (63)	173 (72.4)	0.64 (0.15-2.74)	.54	0.22 (0.03-1.69)	.15
Platelets, ≥300 × 10^9/L	5 (63)	172 (72.0)	0.65 (0.15-2.79)	.56	0.30 (0.04-2.33)	.25
Albumin, ≥3.5 g/dL	5 (63)	201 (84.1)	0.32 (0.07-1.37)	.12	0.31 (0.04-2.49)	.27
AST, ≥100 IU/L	1 (13)	29 (12.1)	1.03 (0.12-8.71)	.98	1.95 (0.13-30.1)	.63
Total bilirubin, ≥1.0 mg/dL	1 (13)	30 (12.6)	1.00 (0.12-8.37)	>.99	1.57 (0.10-24.6)	.75
CRP, ≥10 mg/dL	3 (38)	63 (26.4)	1.68 (0.39-7.22)	.49	3.58 (0.43-29.7)	.24
BNP, ≥40 pg/mL	4 (57)	46 (25.6)	3.88 (0.84-18.0)	.083	1.66 (0.23-12.3)	.62

OR for the continuous variables are interpreted as change in odds per every 1-unit increment for continuous variable.
CAAs were defined as ≥2.5 of Zmax at 4 wk after the onset of Kawasaki disease.

Table VII. Four groups of patients according to CAA at diagnosis and 4 weeks after the onset of Kawasaki disease

Initial Zmax and 4 weeks after Kawasaki disease	A: ≥2.5 to ≥2.5	B: ≥2.5 to <2.5	C: <2.5 to ≥2.5	D: <2.5 to <2.5	*P**				
	n = 9	n = 31	n = 4	n = 281	A vs B	A vs C	B vs C	B vs D	C vs D
Age at onset, mo	10 (3-74)	17 (4-62)	14 (10-24)	25 (0-185)	.077	.14	.68	.13	.16
Age ≥12 mo, n	2 (22)	21 (68)	3 (75)	222 (79.0)	.023	.22	>.99	.17	>.99
Female sex, n	4 (44)	12 (39)	1 (25)	129 (45.9)	>.99	>.99	>.99	.57	.63
Febrile days until the diagnosis, d	6 (3-8)	5 (3-8)	5 (3-8)	5 (2-9)	.60	.70	>.99	.64	.89
Duration of total fever, d	9 (3-18)	5 (3-15)	5 (3-7)	5 (2-25)	.044	.21	.79	.98	.79
Kobayashi score, points	2 (1-8)	3 (0-9)	3 (3-4)	3 (0-10)	.66	.70	.62	.84	.54
Laboratory data at diagnosis									
White blood cell, ×10^9/L	17 (5.9-22)	14 (7.1-27)	12 (6.4-16)	14 (2.9-31)	.34	.090	.34	.58	.16
Neutrophil, ×10^9/L	10 (5.2-18)	8.4 (3.9-18)	7.2 (3.8-7.7)	9.6 (0.82-29)	.64	.17	.087	.27	.045
Lymphocyte, ×10^9/L	5.1 (0.50-11)	3.5 (1.5-8.8)	3.1 (2.3-7.4)	3.0 (0.52-13)	.57	.54	.86	.095	.62
Neutrophil/lymphocyte ratio	1.9 (0.92-10)	2.5 (0.60-7.1)	1.9 (0.92-2.9)	3.2 (0.15-53)	.96	.64	.35	.069	.12
Hgb, g/dL	11 (8.5-13)	11 (8.6-13)	11 (10-11)	11 (8.1-15)	.59	.94	.76	.27	.39
Platelet, ×10^9/L	371 (110-1182)	403 (229-703)	303 (235-682)	361 (99-746)	.88	.36	.41	.19	.55
Albumin, g/dL	4.0 (2.6-4.4)	3.9 (2.1-4.4)	3.7 (3.2-4.3)	3.8 (2.2-5.1)	.96	.94	.45	.30	.70
BNP, pg/mL	73 (9.2-1870)	32 (5.8-177)	36 (11-271)	21 (5.8-614)	.25	.57	.66	.25	.35
Aspartate aminotransferase, IU/L	37 (19-55)	34 (17-825)	48 (33-130)	33 (2.0-1956)	.97	.35	.23	.95	.24
Alanine aminotransferase, IU/L	18 (14-60)	21 (8.0-265)	72 (10-116)	19 (5-961)	.73	.28	.36	.89	.55
Total bilirubin, mg/dL	0.5 (0.2-0.8)	0.6 (0.1-4.6)	0.4 (0.2-2.0)	0.6 (0.2-4.9)	.45	.82	.51	.46	.25
Sodium, mEq/L	135 (133-140)	136 (131-141)	138 (133-140)	136 (128-142)	.60	.58	.26	.38	.21
CRP, mg/dL	7.9 (2.0-12)	6.2 (0.79-31)	13 (2.1-18)	7.4 (0.42-30)	.28	.12	.13	.11	.22
Maximum z score									
Pretreatment	3.28 (2.57-4.79)	2.69 (2.51-4.36)	1.36 (0.96-1.99)	1.43 (−1.03 to 2.48)	.002	.005	.001	<.001	>.99
4 wk later	3.04 (2.60-4.79)	1.36 (−0.15 to 2.44)	3.20 (2.58-3.98)	1.14 (−1.62 to 2.49)	<.001	>.99	.001	.046	.001
Treatment									
Total dose of IVIG, g/kg	4 (2-7)	2 (2-6)	2 (2-2)	2 (2-6)	.11	.076	.22	.38	.28
Period for normalization of CAA									
6 mo, n	5 (56)		3 (75)						
12 mo, n	1 (11)		1 (25)						
>12 mo, n	3 (33)								

Hgb, hemoglobin.
Values are expressed as n (%) or median (range). CAAs were defined as ≥2.5 of Zmax at 4 weeks after the onset of Kawasaki disease.
**P* value <.008 was considered statistically significant after Bonferroni correction for multiple comparison.