

Z-score is a possible predictor of the risk of coronary artery lesion development in patients with Kawasaki disease in Japan

Takayuki Suzuki (✉ tasuzuki@wakayama-med.ac.jp)

Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Nobuyuki Kakimoto

Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Tomoya Tsuchihashi

Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Tomohiro Suenaga

Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Takashi Takeuchi

Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Shoichi Shibuta

Department of Pediatrics, Kinnan Hospital, Tanabe, Japan

Naomi Kitano

Research Center for community Medicine, Wakayama Medical University, Wakayama, Japan,
Department of Public Health, Wakayama Medical University School of Medicine, Wakayama, Japan

Hiroyuki Suzuki

Departments of Pediatrics, Wakayama Medical University, Wakayama, Japan

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Abstract

ABSTRACT Risk factors for coronary artery lesion (CAL) development in patients with Kawasaki disease (KD) include male sex, age <12 months, intravenous immunoglobulin (IVIG) resistance, and delayed diagnosis. We aimed to explore the relationship between CAL development and Z-score. We enrolled 281 patients with KD who were treated with our protocol. Echocardiography was performed in three phases: pre-treatment (P1), post-treatment (P2), and 4 weeks after onset (P3). The highest Z-score of the right, left main, left anterior descending, and left circumflex coronary arteries was expressed as Zmax at each phase. P3-Zmax ≥ 2.5 represented CAL development. Clinical parameters, such as laboratory data and Z-scores, were retrospectively compared between patients with and without CAL development. Sixty-seven patients (23.8%) showed a P1-Zmax ≥ 2.0 , and CAL development occurred in 21 patients (7.5%). Independent risk factors associated with CAL development were P1-Zmax, a ΔZ_{max} (P2-Zmax - P1-Zmax) ≥ 1 , male sex, <12 months of age, and resistant to the first IVIG administration (adjusted odds ratio [95% confidence interval]: 1.98 [1.01–3.92], 4.04 [1.11–14.7], 6.62 [1.33–33.04], 4.71 [1.51–14.68], 5.26 [1.62–17.13], respectively). Using receiver operating characteristic curve analysis, a P1-Zmax ≥ 1.43 detected CAL development with an area under the curve of 0.64 (sensitivity = 81.0%; specificity = 48.1%). Conclusions : Our results suggest that P1-Zmax and a ΔZ_{max} (P2-Zmax - P1-Zmax) ≥ 1 may predict CAL development.

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis occurring in infants and children, especially those younger than 5 years of age [1]. The most serious complication of KD is coronary arteritis, resulting in coronary arterial dilatation, aneurysm and stenosis. Risk factors for coronary artery lesion (CAL) development in patients with Kawasaki disease (KD) include male sex, age <12 months, intravenous immunoglobulin (IVIG) resistance, and delayed diagnosis [2-6]. Therefore, coronary artery lesion (CAL) is now the leading cause of acquired heart disease in children in developed countries.

As the etiology of KD is still unknown, radical treatments to prevent CAL development in patients with KD are not available. Recently, intensified initial standard steroid [7] and cyclosporin A (CsA) [8] therapy have contributed to a decrease in the incidence of CAL. However, the actual number of patients with CAL have not decreased because the incidence of KD continues to increase in Japan [9]. Therefore, it is vital to identify predictive markers of CAL development before treatment.

In recent times, Z-score has been used to evaluate CAL in patients with KD [10,11]. American Heart Association (AHA) guidelines [12] recommend intensified initial treatment for patients considered to be at a high risk for CAL. Several studies [13-16] have shown that CAL development may be predicted using pre-treatment Z-score ; however, this has not yet been shown in Japan.

In the present study, we aimed to predict CAL development using Z-scores in patients with early acute phase of KD to enable early intervention with intensified therapy and we serially examined coronary artery

Z-scores in patients with KD at different time points from admission (pre-treatment) to 1 month after onset. We analyzed how Z-scores in the early acute phase of KD may correlate with Z-scores 1 month after KD onset; that is, the coronary arterial sequelae of KD.

Methods

Study population

A total of 324 patients who fulfilled the diagnostic criteria for KD and who were admitted to our hospital to undergo our treatment protocol from March 2009 to March 2018 were enrolled. The diagnosis of KD was made in accordance with the criteria from the 5th Diagnostic Guidelines established by the Japan Kawasaki Disease Research Committee [17]. Day 1 of KD was defined as the first day of fever (axillary temperature $\geq 37.5^{\circ}\text{C}$). The study was approved by the ethics committee of Wakayama Medical University (No: 2801). Patients who fulfilled at least one of the following criteria were excluded: 1) no IVIG treatment or not following our treatment protocol; 2) recurrent KD; 3) follow-up echocardiographic measurements not available; 4) patients who might have an effect on Z-scores, such as a high body mass index (≥ 25), a history of cardiovascular disease, systemic arterial hypertension, and other syndromes, such as Noonan/LEOPARD syndrome. All enrolled patients underwent our treatment protocol: IVIG (2 g/kg/day for 24 hours) + aspirin (30mg/kg/day) (first-line therapy). If patients were resistant to IVIG after the first administration (persistent or recrudescence fever ((axillary temperature $\geq 37.5^{\circ}\text{C}$) 24 hours after the first IVIG administration), they were treated with additional IVIG (2 g/kg/day for 24 hours) as a second-line therapy. In addition, patients who were resistant to the second IVIG administration (persistent or recrudescence fever (axillary temperature $\geq 37.5^{\circ}\text{C}$) after completion of IVIG) were treated with oral CsA (5 mg/kg/day) as a third-line therapy. The medical records of all enrolled patients were retrospectively reviewed, including demographics, clinical characteristics, medications, serial echocardiographic findings, and laboratory tests on admission, such as white blood cell count (WBC), percentage of neutrophils, hematocrit (Ht), platelet count (Plt), aspartate aminotransferase (AST), serum albumin (Alb), serum sodium (Na), and C-reactive protein (CRP). Laboratory data were converted into categorical variables based on the previous scoring system for KD [18-21].

Evaluation of coronary artery Z-score

Echocardiography was performed using the Philips EPIQ7 or iE33 echocardiographic machine (Philips, Eindhoven, Netherlands) and a sector probe with a frequency of 8 MHz. Three pediatric cardiologists measured the inner diameter of the right coronary artery (RCA), left main coronary artery (LMCA), left anterior descending artery (LAD), and left circumflex artery (LCX), and the measurements were performed in three phases: pre-treatment (P1; at the time of KD diagnosis or before IVIG treatment), post-treatment (P2; after 1st IVIG treatment and around 10 days from KD onset), and the convalescent phase (P3; around 4 weeks from KD onset). We measured internal coronary artery diameter twice at the end of the T wave as the maximum diameter [22] and calculated an average value. Z-scores were retrospectively calculated for each four coronary artery dimensions using the Z-score calculator (Version 4.0 Full, LMS_Z_Score)

[11,23]. Body surface area (BSA) calculated using the Haycock formula. As the four coronary artery segments need to be evaluated in patients with KD, the highest Z-score of these four segments was expressed as Zmax in each phase. As multiple echocardiograms were performed in the P2 phase, we used the highest Z-score (P2-Zmax) during this phase. In addition, we calculated the difference between P2-Zmax and P1-Zmax to examine the change in Z-score (ΔZ_{max}) after IVIG treatment. A P3-Zmax ≥ 2.5 denoted CAL development.

Statistical analysis

Continuous variables are presented as median (interquartile range: IQR), and categorical variables are presented as frequency and percentage. All statistical analyses were performed using JMP Pro version 14 (SAS Institute Japan Ltd., Tokyo, Japan). Associations between two groups were analyzed using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Multivariate logistic regression analysis was used to assess the independent predictors of CAL development. Moreover, the odds ratio (OR) and 95% confidence interval (CI) were calculated. We also confirmed no significant multicollinearity between the explanatory variables. A predictor of P1-Zmax for CAL development was determined by receiver operating characteristic (ROC) analysis. Differences with a two-tailed *p* value of <0.05 were considered statistically significant.

Results

Patient characteristics

A total of 324 patients were diagnosed with KD at our hospital during the study period. Based on the exclusion criteria, we excluded patients who did not follow our treatment protocol ($n = 16$), patients with recurrent KD ($n = 12$), and patients without follow-up echocardiographic measurements ($n = 15$). There were not patients who might have an effect on Z-scores. A total of 281 patients were enrolled in the study (Figure 1). All patients were treated within 9 days of KD onset. In terms of treatment response, 177 patients responded to the first IVIG administration, 45 patients responded to additional IVIG administration, and 59 patients (21.0%) did not response to either initial or additional IVIG administration. The latter cohort of patients received CsA as a third-line therapy. Characteristics, clinical data, treatment data, and echocardiographic data of all enrolled patients stratified by presence or absence of CAL are shown in Table 1. There was a significantly greater number of male children in the group with CAL compared with the group without CAL (Table 1). The age range of patients with KD was 1 month to 10 years (median, 23 months). There was a significantly greater number of children <12 months of age in the group with CAL compared with the group without CAL. As for laboratory data, serum Alb concentration ($Alb \leq 3.5$ g/dL) was significantly lower during the pre-treatment phase in the group with CAL compared with the group without CAL. As for the number of illness days before initiating the 1st IVIG treatment, there was no significant difference between the two groups. However, a significantly greater number of patients were resistant to the first IVIG administration and additional IVIG administration in the group with CAL compared with the group without CAL.

Echocardiographic data

All four coronary artery dimensions were measured in 281 cases, with the exception of LAD and LCX artery dimensions in P1, which were measured in 265 cases and 243 cases, respectively. The P1-Zmax in the group with CAL was significantly higher compared with the group without CAL. In addition, there was a significantly greater number of patients with a $\Delta Z_{\max} \geq 1$ in the group with CAL compared with the group without CAL (Table 1).

Serial changes in the Z-score of the four segments are shown in Figure 2. The contributions of each segment and each phase to Zmax in the group with CAL are indicated by ▲ and ●. The ▲ symbol indicates the Zmax of patients with CAL who did not respond to two IVIG administrations and who were thus treated with CsA. The ● symbol shows patients with CAL who responded to either the first or additional IVIG treatments. In all phases, either the RCA or the LMCA mainly contributed to Zmax in patients with CAL. The contributions of the RCA and the LMCA to Zmax in each phase were as shown by the following ratios: P1: 17/21 (81.0%); P2: 16/21 (76.2%); P3: 17/21 (81.0%). In addition, serial changes in P1-Zmax, P2-Zmax, and P3-Zmax in all patients are shown in Figure 3. The median P1-Zmax, P2-Zmax, and P3-Zmax were 1.54 (IQR: -0.48 to +4.51), 1.84 (IQR: +0.52 to +7.86), and 1.42 (IQR: +0.02 to +6.42), respectively. Sixty-seven patients (23.8%) had a P1-Zmax ≥ 2.0 . The relationships between P1-Zmax and ΔZ_{\max} in patients with and without CAL are shown in Figure 4. A P1-Zmax ≥ 2 was not a predictor of CAL, but a $\Delta Z_{\max} \geq 1$ was a strong predictor of CAL development (Table 1). Moreover, only 5 of 67 patients with a P1-Zmax ≥ 2 had a $\Delta Z_{\max} \geq 1$.

Independent risk factors for CAL development and ROC analysis

We identified six potential risk factors associated with CAL development with a univariate analysis: male sex ($p = 0.002$), age <12 months ($p = 0.022$), serum Alb concentration ≤ 3.5 g/dL ($p = 0.031$), resistance to initial IVIG administration ($p < 0.001$), P1-Zmax ($p = 0.035$), and a $\Delta Z_{\max} \geq 1.0$ ($p = 0.007$) (Table 1). Multivariate logistic regression was subsequently conducted to assess the independent effects of the six factors of CAL development. P1-Zmax ($p = 0.047$), $\Delta Z_{\max} \geq 1.0$ ($p = 0.034$), male sex ($p = 0.021$), <12 months of age ($p = 0.007$), and resistance to initial IVIG administration ($p = 0.005$) were independent risk factors for CAL development (Table 2). Furthermore, in the ROC curve analysis, the area under the ROC curve of P1-Zmax to predict CAL development was 0.64. The optimal cutoff value for P1-Zmax was 1.43 with a sensitivity of 81.0% and a specificity of 48.1% (Figure 5).

Discussion

Although there are three predictive scores for IVIG resistance in patients with KD in Japan [18-20], there are currently no indicators to predict CAL before IVIG treatment. In this study, we identified five independent predictive factors for CAL development in patients with KD: P1-Zmax, a $\Delta Z_{\max} \geq 1$, male sex, <12 months of age, and resistance to the first IVIG administration. Although male sex, <12 months of age, and resistance to initial IVIG administration as risk factors for CAL development have been previously reported [2-6], P1 Z-score ≥ 1.43 and a $\Delta Z_{\max} \geq 1.0$ are novel predictors of CAL development

in Japan. Evaluating serial changes in Z-score from pre-treatment to post-treatment provides important information that can aid in the choice of initial and additional treatments in high-risk patient groups.

CAL in patients with KD are associated with pathological changes in the coronary artery wall. Based on an analysis of autopsy cases, edematous changes in the media are seen in the early stages of KD [24], and coronary artery dilatation may also occur in the early stages of KD onset. As the evaluation of Z-score using echocardiography can consecutively recognize changes in coronary artery dimensions, it is possible that echocardiography may be more accurate than pathological observations for the prediction of CAL development in patients with KD.

The Z-score is an index of coronary artery dimensions that is standardized to sex and BSA. Therefore, the Z-score may be useful for direct and sensitive detection of early coronary artery dilatation compared with clinical findings, such as fever and serum CRP concentration. Fuse et al. reported that 23.4% of patients showed coronary artery dilatation ($Z\text{-score} \geq 2.0$) after 5 days of illness during the pre-treatment phase [25], which is consistent with our findings (67/281, 23.8%).

Several studies [13-16] have shown that CAL development may be predicted using the P1 Z-score; however, this has not yet been shown in Japan. These studies reported that a P1-Zmax ≥ 2.0 is better than that of IVIG resistance for predicting CAL development. In addition, Dionne et al. reported that intensified initial therapy with steroids or infliximab in patients with a P1 Z-score ≥ 2.0 might prevent progression of coronary arterial dilatation [15]. Thus, if the P1 Z-score can predict CAL development and progression, it will be useful for pediatricians when selecting initial therapies, including intensified therapies. However, many patients in our study with a P1-Zmax ≥ 2.0 did not develop CAL (Figure 4). In other words, a P1-Zmax ≥ 2.0 had a low positive predictive value for predicting CAL (7/60, 11.7%). There are two possible reasons why our results are different compared with those of other studies. First, the number of days of illness at which 1st IVIG was administered in other studies was greater than in our study. Although the median number of illness days at which 1st IVIG was administered in a previous report was approximately 7 [13-16], the median in our cohort was 4 (IQR: 4–5). Therefore, there is an interval of approximately 3 days in terms of the number of days of illness at which P1 Z-score was measured in our cohort versus other studies. In the Nationwide Survey in Japan [4], the median number of illness days at which initial IVIG was administered was also 5 (IQR 4–6). Patients with Kawasaki disease in Japan tend to start treatment earlier compared with patients in other studies. Fuse et al. reported that 42.9% of patients showed coronary artery dilatation ($Z\text{-score} \geq 2.0$) after 7 days of illness during the pre-treatment phase, but only 11% of patients showed coronary artery dilatation ($Z\text{-score} \geq 2.0$) after 4 days of illness according to the cumulative probability curve [25]. Thus, it may not be appropriate to predict CALs at a P1-Zmax ≥ 2.0 in cases where treatment is started earlier. Second, the treatment protocol is a very important factor for coronary outcomes and CAL development. Our treatment protocol included IVIG (first line), IVIG (second line), and CsA (third line), without using the predictive score of IVIG resistance. A total of 60 of 67 patients with a P1-Zmax ≥ 2 showed a $\Delta Z\text{max} < 1$ (Figure 4). It is very interesting that most patients with coronary artery dilatation, in spite of the number of early illness days, did not develop CAL. It is possible that our protocol may be effective for patients with severe KD and dilatation in the

early acute phase. From the above, it is clear that a different predictor with a $P1-Z_{max} \geq 2$ is needed. A total of 46 of 214 patients (21.5%) with a $P1-Z_{max} < 2$ showed a $\Delta Z_{max} \geq 1$ (Figure 4) and $\Delta Z_{max} \geq 1$, even after treatment, which were strong predictors of CAL development ($p=0.007$, Table1). These data suggest another important point; Some patients with a $P1-Z_{max} < 2$ may be treated with intensified initial therapy.

We attempted to examine the cutoff of $P1-Z_{max}$ for CAL development using ROC curve analysis. A $P1-Z_{max} \geq 1.43$ detected CAL development with an area under the ROC curve of 0.64 (sensitivity = 81.0%; specificity = 48.1%). Although the specificity of a $P1-Z_{max} \geq 1.43$ was only 48.1% for predicting CAL development, the sensitivity was as high as 81.0%. A Z score < 2.0 is usually in the normal range, but Fuse et al. reported that a $P1-Z_{max} \geq 1.5$ was present in 30.1% of patients by 5 days of illness, 58.4% by 7 days of illness, and 79.0% by 10 days of illness [25]. According to the statistical normal distribution, a Z-score ≥ 1.5 is considered normal in 6.7%. Thus, Fuse et al. also calculated the positive predictive value of $P1-Z_{max} \geq 1.5$ was 0.777 after 5 days of illness [25]. This may indicate that some patients with acute KD who have been treated by 5 days of illness and have a $P1-Z_{max} \geq 1.5$ are at risk of CAL development.

Based on the results of the present study, we propose that patients with a $P1-Z_{max} \geq 1.43$ should be treated with intensified initial therapy using CsA or steroids due to its high sensitivity to predict CAL development. In addition, patients with a $\Delta Z_{max} \geq 1$ should also be treated with an intensified protocol when one is identified. It is possible that these two steps in the treatment strategy could reduce the incidence of CAL.

Study limitations

There are several limitations of the present study that should be highlighted. First, this study adopted a retrospective design and was carried out at a single institution. Moreover, the sample size was small because many patients were excluded to simplify the inclusion of different conditions. Thus, further multi-center studies should be performed to confirm the findings. Second, the treatment protocol used in this study was our protocol only, and other treatment protocols may demonstrate different rates of CAL development. Third, we could not detect all coronary artery segments in all phases. Fourth, the Z-score formula used in this report is different from the previous report. Thus, comparisons should be made with caution. Fifth, four coronary artery branches were measured in accordance with Japanese guidelines [17]. The AHA recommends not to rely on LMCA values, but to use RCA and LAD values instead. In the dominant left coronary artery situs or the dominant right coronary artery situs, patients can be considered as having a $P1-Z_{max} > 1.43$.

Conclusions

Independent risk factors associated with CAL development were $P1-Z_{max}$, a $\Delta Z_{max} \geq 1$, male sex, < 12 months of age, and resistance to the first IVIG administration. In addition, using a ROC curve analysis, a $P1-Z_{max} \geq 1.43$ detected CAL development with an area under the ROC curve of 0.64 (sensitivity = 81.0%; specificity = 48.1%). For patients with these risk factors, we need to consider the best approach for

intensified initial treatment. Further investigations will be needed in patients receiving alternative initial treatments.

Declarations

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Conflict of interest The authors declare that there is no conflict of interest.

Abbreviations

CAL Coronary artery lesion

CsA Cyclosporin A

IVIG Intravenous immunoglobulin

KD Kawasaki disease

LAD Left anterior descending artery

LCX Left circumflex artery

LMCA Left main coronary artery

P1 Pre-treatment phase (at the time of KD diagnosis or before IVIG treatment)

P2 Post-treatment phase (after 1st IVIG treatment and around 10days from KD onset)

P3 The convalescent phase (around 4 weeks from KD onset)

RCA Right coronary artery

Zmax The highest Z-score of four segments of coronary artery

ΔZ_{max} Difference between P2-Zmax and P1-Zmax

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Tables

Due to technical limitations, tables 1 and 2 can be found as downloads in the supplementary files.

Figures

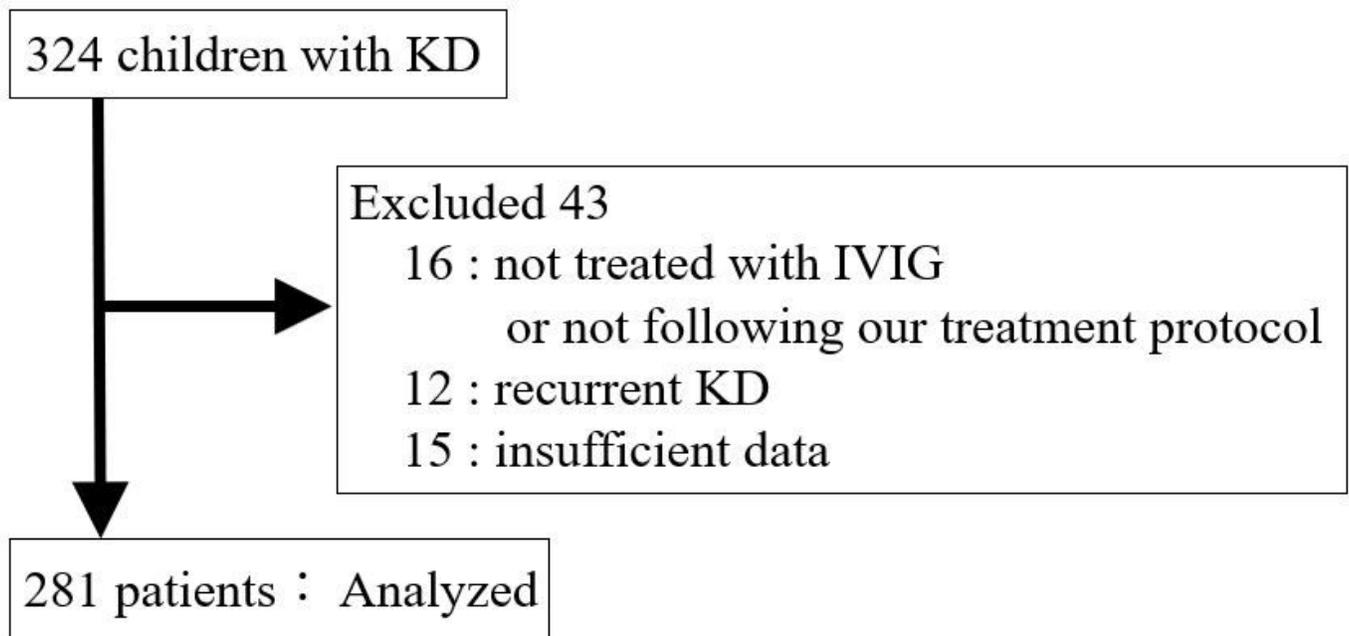


Figure 1

Study flow chart. IVIG, intravenous immunoglobulin; KD, Kawasaki disease

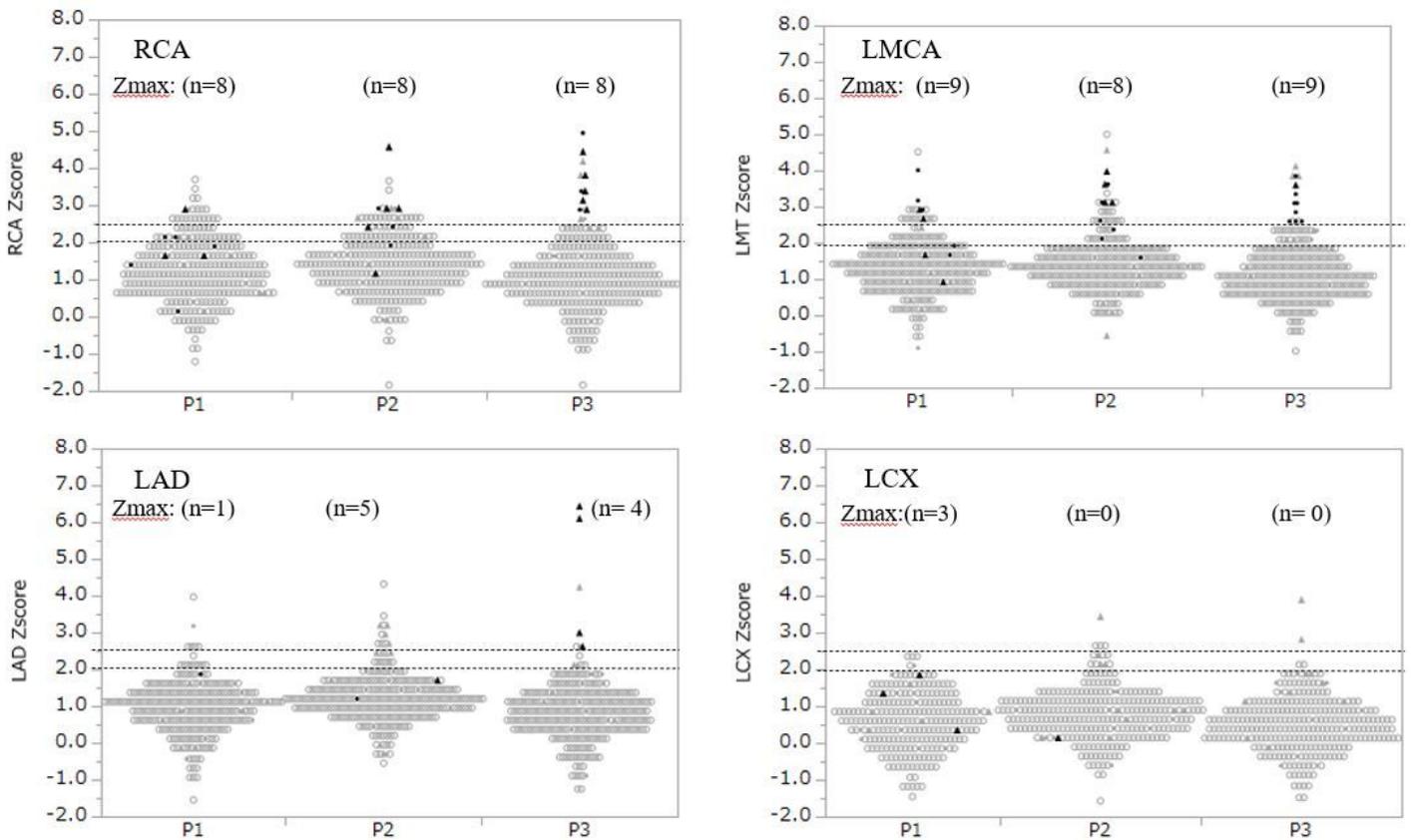


Figure 2

Z-scores of the four segments before and after intravenous immunoglobulin (IVIG) treatment. P1, pretreatment (at the time of KD diagnosis or before IVIG treatment); P2, post-treatment (around 10 days from KD onset); P3, the convalescent phase (around 4 weeks from KD onset); RCA, right coronary artery (left upper); LMCA, left main coronary artery (right upper); LAD, left anterior descending artery (left bottom); LCX, left circumflex artery (right bottom). n = number of patients. ▲ and ● show the maximum coronary artery Z-score (Zmax) of patients with coronary artery lesion (CAL) in each phase. ▲ indicates the Zmax of patients with CAL who did not respond to two IVIG administrations and who were thus treated with cyclosporin A (CsA). ● shows patients with CAL who responded to either the first or additional IVIG administration. ◻ shows patients without CAL. In all phases, either the RCA or the LMCA contributed to Zmax in patients with CAL (P1: 17/21; P2: 16/21; P3: 17/21).

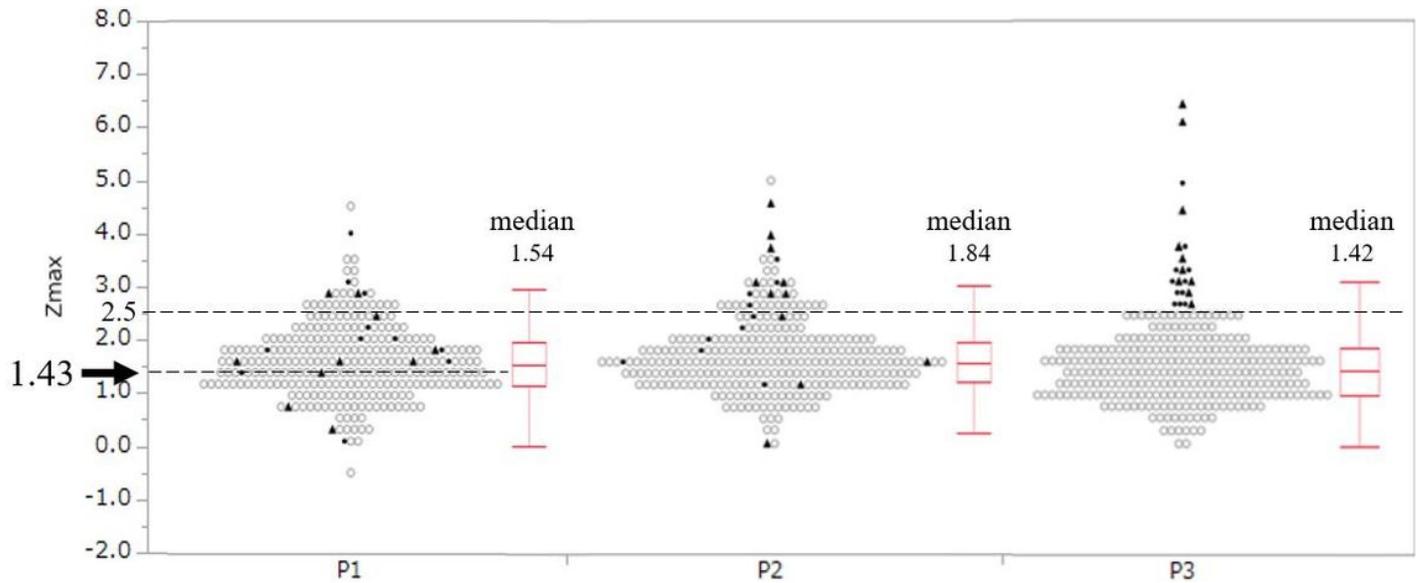


Figure 3

Maximum coronary artery Z-score (Z_{max}) of the four segments before and after intravenous immunoglobulin (IVIG) treatment. P1, pretreatment (at the time of KD diagnosis or before IVIG treatment); P2, post-treatment (around 10 days from KD onset); P3, the convalescent phase (around 4 weeks from KD onset). The median P1- Z_{max} , P2- Z_{max} , and P3- Z_{max} were 1.54 [IQR: -0.48 to 4.51], 1.84 [IQR: +0.52 to +7.86], and 1.42 [IQR: +0.02 to +6.42], respectively. Sixty-seven patients (23%) showed a P1- $Z_{max} \geq 2.0$. ▲ indicates the Z_{max} of patients with coronary artery lesion (CAL) who did not respond to two IVIG administrations and who were thus treated with cyclosporin A (CsA). ● shows patients with CAL who responded to either the first or additional IVIG administration. ◻ shows patients without CAL.

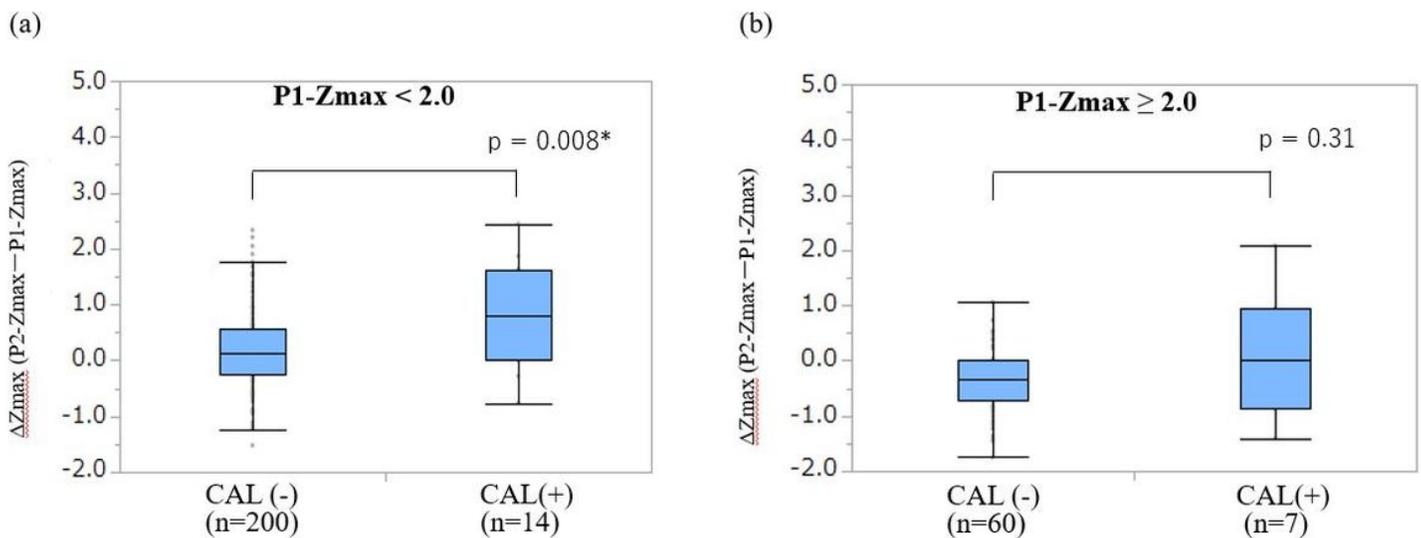
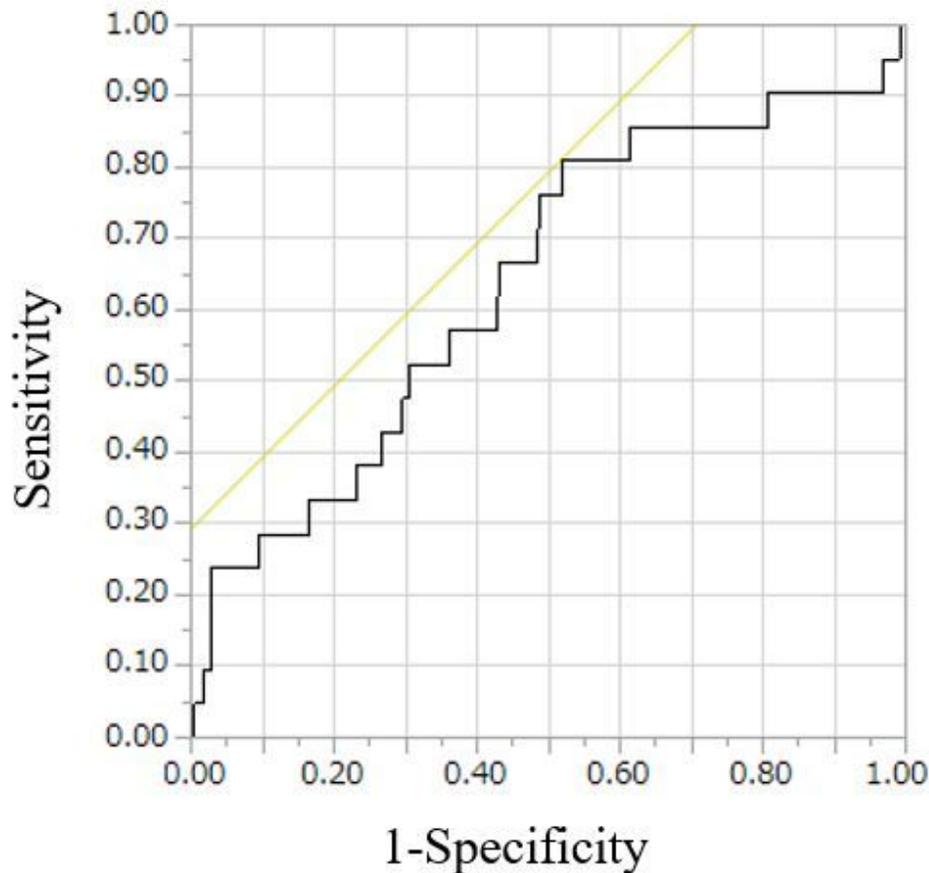


Figure 4

P1-Zmax, and ΔZ_{max} ($P2-Z_{max} - P1-Z_{max}$) in patients with and without coronary artery lesion (CAL). *Analyzed by a Fisher's exact test or a Mann-Whitney U test. $p < 0.05$ P1-Zmax, pretreatment maximum coronary artery Z-score; P2-Zmax, post-treatment (around 10 days from KD onset) maximum coronary artery Z-score; P3-Zmax, convalescent phase (around 4 weeks from KD onset) maximum coronary artery Z-score; n = number of patients. Left/Right panels show the relationship between a $P1-Z_{max} \geq 2 / < 2$, ΔZ_{max} ($P2-Z_{max} - P1-Z_{max}$), and CAL (+/-). (a) Left panel: $P1-Z_{max} < 2$ Vertical axis: ΔZ_{max} ($P2-Z_{max} - P1-Z_{max}$); horizontal axis: patients without CAL ($P3-Z_{max} < 2.5$, n = 200) and with CAL ($P3-Z_{max} \geq 2.5$, n = 14). (b) Right panel: $P1-Z_{max} \geq 2$ Vertical axis: ΔZ_{max} ($P2-Z_{max} - P1-Z_{max}$); horizontal axis: patients without CAL ($P3-Z_{max} < 2.5$, n = 60) and with CAL ($P3-Z_{max} \geq 2.5$, n = 7). Left panel (a) shows the relationship between CAL (+/-) and ΔZ_{max} ($P2-Z_{max} - P1-Z_{max}$) in patients with a $P1-Z_{max} < 2.0$, and the right panel (b) shows the relationship between CAL (+/-) and ΔZ_{max} ($P2-Z_{max} - P1-Z_{max}$) in patients with a $P1-Z_{max} \geq 2.0$.



Value	Sensitivity	Specificity	AUC
1.43	81.0%	48.1%	0.64

Figure 5

Receiver operating characteristic (ROC) curve of pretreatment maximum coronary artery Z-score (P1-Zmax) for predicting coronary artery lesion (CAL). The optimal cutoff value for P1-Zmax was 1.43 with a sensitivity of 81.0% and a specificity of 48.1%. AUC, area under the curve.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TSuzukiTable1.pptx](#)
- [TSuzukiTable2.pptx](#)