

Heart rate, Responsiveness to Intravenous Immunoglobulin, and Coronary Artery Aneurysms in Kawasaki disease

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ABSTRACT

Objective

To evaluate whether heart rate (HR) was associated with intravenous immunoglobulin (IVIG) responsiveness or development of coronary artery lesions (CALs) in patients with Kawasaki disease.

Study design

We conducted a retrospective cohort study using data from in patients with Kawasaki disease who were hospitalized in our institution from 2006 to 2016. The patients were divided into 5 groups according to the age- and temperature-adjusted HR z score ($HRZ_{age/temp}$) just before IVIG administration. The ORs of outcomes were estimated by using logistic regression models, with the middle group set as the reference.

Results

Of the 322 patients, a total of 98 patients (30%) were refractory to initial IVIG treatment. The patients whose $HRZ_{age/temp}$ belonged to the lowest group were at the highest risk of being refractory to the initial IVIG treatment (OR 2.10 [95% CI 1.01-4.37]). Multivariable analyses showed the same trend, though this was not statistically significant. The patients with the highest $HRZ_{age/temp}$ were most likely to develop CALs (OR 2.61 [95%CI 0.86-7.92]).

Conclusion

In patients with Kawasaki disease, HRs has a different relationship with IVIG responsiveness and CALs. Low $HRZ_{age/temp}$ might be associated with high risk of being refractory to the initial IVIG

treatment, while the risk of developing CALs increased among those whose HRs were high. Further studies are necessary to investigate the mechanisms regarding HR and these outcomes in Kawasaki disease.

Kawasaki disease is an acute febrile illness in childhood characterized by bilateral conjunctivitis, redness of the lips and oral mucosa, cervical lymphadenopathy, rash, and change in the extremities. High-dose intravenous immunoglobulin (IVIG) has been established as the first-line treatment for patients with Kawasaki disease in the acute phase for its effectiveness in reducing the inflammation and the occurrence of coronary artery lesions (CALs).¹⁻³ However, 10%-20% of patients are refractory to the initial IVIG treatment.⁴⁻⁶ These patients tend to have fever for longer periods and are considered to be at high risk of presenting with CALs.⁴⁻⁶ Therefore, the prediction of unresponsiveness to the initial IVIG and treatment stratification has emerged as an important issue in this era.

Several studies on clinical prediction rules for IVIG responsiveness have been published; Kobayashi et al developed a prediction rule for responsiveness to the initial IVIG treatment, which was validated and showed high discriminative ability.⁷ Egami et al reported a good discrimination of nonresponders among patients with Kawasaki disease treated with IVIG using this model.⁸ Other studies described the potential for stratifying patients with Kawasaki disease to provide more aggressive treatments to those who are likely to be resistant to IVIG treatment.^{9,10} The published prediction models are based on patients' age, the clinical day of IVIG treatment, and laboratory findings, such as platelet count, C-reactive protein, or liver enzymes.

Heart rate (HR) is a simple approach to assessing the status of pediatric patients. HR is a principal component of various diagnostic criteria such as systemic inflammatory response syndrome,¹¹ clinical tools such as triage systems in emergency department,^{12,13} or early warning systems for hospitalized patients.^{14,15} Although HR has been widely shown to be a useful predictor in pediatric care, its utility in patients with Kawasaki disease has not been clarified so far. The principal aim of this study was to elucidate the association between HR and responsiveness to the initial IVIG

treatment in Kawasaki disease. We also investigated its association with the development of CALs.

METHODS

This study was a retrospective cohort study that used the clinical records of patients with Kawasaki disease who were hospitalized in Kobe City Medical Center General Hospital from April 2006 to March 2016. Patients who were diagnosed with Kawasaki disease in the acute phase and treated with IVIG (2g/kg) were included in this study.

According to the *Diagnostic Guidelines for Kawasaki Disease (5th revision)*,¹⁶ patients are diagnosed with typical Kawasaki disease if they have a fever and at least 4 of the 5 principal features (change in extremities, polymorphous exanthema, conjunctival injection, changes in lips and oral cavity, cervical lymphadenopathy), or if they have a fever and 3 principal features with coronary artery abnormalities detected. In this study, we also included patients with Kawasaki disease who had a fever and 3 principal features without coronary artery abnormalities (“incomplete Kawasaki disease”) unless other diseases mimicking Kawasaki disease were verified by laboratory findings because inclusion of incomplete Kawasaki disease was considered clinically relevant. Patients were excluded if the initial IVIG treatment had already started before admission to our hospital, if treatments except for aspirin or other antiplatelet drugs were given together with the initial IVIG treatment, or if data pertaining to vital signs were missing. For recurrent patients with Kawasaki disease, only the data for the first hospitalization were included.

The study protocol was approved by the Ethics Committee of Kyoto University, Graduate School and Faculty of Medicine (R0538) and Kobe City Medical Center General Hospital (no.160604). Because the number of sampling points for vital signs varied from patient to patient, we used the data before IVIG was started. HRs were extracted from electrocardiogram for monitoring, and

axillary temperatures were recorded. Using the formula that Daymont et al reported (the calculation table was obtained from the author through personal communication),¹⁷ Heart rate was adjusted for age and body temperature, and given as a z score (age- and temperature- adjusted HR z score [$HRZ_{age/temp}$]).

The primary outcome of this study was responsiveness to the initial IVIG treatment. Patients were defined as being responsive to the IVIG treatment or “responders” if the temperature dropped and stayed below 38.0°C within 24 hours after IVIG had ended. The secondary outcome was the presence of CALs including transient dilatation of coronary arteries. Coronary arteries were considered abnormal when examinations by 2-dimensional echocardiography showed that internal lumen diameters were ≥ 3 mm in patients < 5 years old, ≥ 4 mm in patients ≥ 5 years old, or $> +2.5$ SD for patients’ body surface area.

The following data were collected just before initial IVIG was started: white blood cell count, percentage of neutrophils (% neutrophil), hematocrit, platelet count (PLT), serum concentrations of C-reactive protein (CRP), serum sodium, aspartate aminotransferase (AST), alanine aminotransferase, total bilirubin, and serum albumin.

Statistical Analyses

Patient characteristics were described by numbers and percentages for the categorical variables, and medians and IQRs for the continuous variables. The distribution of variables was compared by the Welch t test or Fisher exact test between patients who showed response to the initial IVIG treatment and those who did not.

According to $HRZ_{age/temp}$, the patients were divided into 5 groups at the quintile points, labeled as group 1 (those with the lowest $HRZ_{age/temp}$) to group 5 (those with the highest $HRZ_{age/temp}$). ORs

for the outcomes were calculated using multiple logistic regression models using group 3 as the reference group. We constructed 4 models including different variables from the following candidates: sex, clinical day of the initial IVIG treatment, white blood cell count, % neutrophil, hematocrit, PLT, CRP, sodium, AST, total bilirubin, and albumin. Model 1 contained only $HRZ_{age/temp}$ as the explanatory variable (crude model); model 2 further included clinical day of the initial IVIG treatment, % neutrophil, PLT, CRP, sodium, and AST (these variables were all included in the Kobayashi score⁷); model 3 contained the same variables as model 2 plus total bilirubin (included in another prediction rule¹⁸), hematocrit and albumin (these variables might affect intravascular volume status); and model 4 included all the candidate variables above (full model). Because the data for several variables were considerably lacking, we conducted multiple imputations by chained equations for these data.

For sensitivity analyses, we conducted multivariable analyses using the models that included the patients' age as the explanatory variable so that the adjusting method could not remove the dependencies of HR on age. We also performed sensitivity analyses using only the data of typical patients with Kawasaki disease, or the data from those without any missing data.

Wald tests were used to obtain *P* values. All reported *P* values were 2-tailed, and *P* values of less than .05 were considered statistically significant. R (v 3.4.2, R Development Core Team, Vienna, Austria) was used for all analyses.¹⁹

RESULTS

During the study period, a total of 501 patients with Kawasaki disease were hospitalized. Of the 501 patients, 107 patients were excluded; 48 patients were likely to have other diseases mimicking Kawasaki disease; 21 patients were not in the acute phase; 16 patients repeatedly suffered from

Kawasaki disease on 2 occasions or more (only the first hospitalization was included in these patients); in 14 patients, essential data were missing; and in 8 patients, the initial IVIG treatments had already started in other institutions. Of the 394 eligible patients, 322 were given IVIG treatment and included in the analyses (Figure 1).

Of the 322 patients given the initial IVIG treatment at our institution, 224 patients were defined as responsive to the initial IVIG treatment, and the remaining 98 patients were regarded as nonresponders. Table 1 shows the baseline characteristics of IVIG responders and nonresponders. The median $HRZ_{age/temp}$ among the nonresponders was -0.10, which was lower than that of the responders (median 0.26, $P = .006$). There were also statistically significant differences between the responders and nonresponders in the distributions of age, sex, % neutrophil, CRP, serum sodium, AST, and total bilirubin. The proportion of patients who presented with CALs was significantly higher among the nonresponders than the responders (17% and 7%, respectively). The median $HRZ_{age/temp}$ among the patients with CALs and those without CALs were 0.63 and 0.11, respectively ($P = .16$). The characteristics of patients according to the groups by $HRZ_{age/temp}$ are described in Table 2 (available at www.jpeds.com).

As described in Table 3 (available at www.jpeds.com) and Figure 2, patients whose $HRZ_{age/temp}$ belonged to the lowest group (group 1) were at highest risk of being refractory to the initial IVIG treatment. The OR (with 95% CI) for those unresponsive to IVIG in group 1 compared with the reference group (group 3) was 2.10 (1.01-4.37) in the crude model (model 1). The other models also revealed similar trends, though these were not statistically significant.

The results of multivariable analyses for CALs are shown in Table 4 (available at www.jpeds.com) and Figure 3. Unlike the results of IVIG responsiveness, the patients with the highest $HRZ_{age/temp}$ (group 5) were at higher risk of presenting with CALs compared with the other groups including

group 1, which was considered to be at high risk of being refractory to the initial IVIG treatment as previously mentioned. When using the crude model (model 1), the OR (95% CI) for those presenting with CALs among group 5 compared with group 3 was 2.61 (0.86- 7.92). The HR corresponding to the quintile points of $HRZ_{age/temp}$ are shown in Table 5 (available at www.jpeds.com).

When plotting $HRZ_{age/temp}$ against body temperature, $HRZ_{age/temp}$ had no apparent association with body temperature. However, the plot of $HRZ_{age/temp}$ and age suggested that there still remained an inverse relationship, which indicated that patients' age appeared to be an important covariate (Figure 4; available at www.jpeds.com). Even after adding the patients' age to the models, the patients in group 1 remained at the highest risk of being refractory to the initial IVIG treatment, and those in group 5 were still most likely to develop CALs (Tables 6 and 7; available at www.jpeds.com).

We performed a sensitivity analysis using only the data from patients with typical Kawasaki disease, or only the data without missing values, which indicated similar results (Tables 8–11; available at www.jpeds.com).

DISCUSSION

The patients with the lowest $HRZ_{age/temp}$ (group 1) were at the highest risk of being refractory to the initial IVIG treatment (OR 2.1 [95% CI 1.0-4.4], group 3 as the reference group). This tendency remained even after adjusting for the factors known as predictors for IVIG responsiveness, or factors possibly associated with intravascular volume status.

Although there are no plausible explanations why relative bradycardia was associated with increased risk of being unresponsive to IVIG, the interaction between systemic inflammatory

response and activity of the autonomic nerve system might be involved.²⁰ HR is decreased by vagus nerve activity, and it is increased by activation of the sympathetic nervous system. A large number of studies using data from animals and humans show that vagal activity regulates inflammation and prevents tissue damage from an excessive inflammatory response.²¹ We speculated that vagus nerve activity might be increased in group 1, which could counterbalance as the anti-inflammatory response.

With respect to the occurrence of CALs, Suzuki et al reported that marked tachycardia was a potential risk indicator for CALs in Kawasaki disease.²² In the study, the mean HR during the fever period was significantly higher among the patients who presented with CALs after adjusting for potential confounders such as age, duration of febrile period, hematocrit, and CRP. A similar observation was described in our study. The relationship between HRs and the development of CALs differed from the relationship between HRs and responsiveness to the initial IVIG treatment. Instead of group 1, the patients with the highest HRs (group 5) were at increased risk of developing CALs.

There are several possible explanations for the dissociation between IVIG responsiveness and occurrence of CALs in terms of association with patient HRs. First, among the patients who were defined as IVIG nonresponders, clinical course might have not been homogeneous. Some patients had persistent fever, then required additional treatments; others only had transient fever and no extra treatment were given. On the other hand, some patients who were defined as responsive to the initial IVIG treatment could have had ongoing Kawasaki disease symptoms. In our study, 66% (19 of 29) of IVIG nonresponders were given the second IVIG treatment in group 1; whereas in group 5, over 90% (17 of 18) of IVIG nonresponders needed the additional IVIG treatment (Table II), though the interpretation of this result might be difficult because indication for treatment was

determined on the basis of various factors. More precise definition of IVIG responsiveness, based on more detailed clinical observation (eg, the extent of fever, timing of recurrence, or other Kawasaki disease symptoms), may reinforce the value of HR in patients with Kawasaki disease. Second, the development of CALs depends not only on the patient condition but also on the treatments given after the initial IVIG, or possibly on the timing of the initial IVIG administration. Obviously, HR before the initial IVIG treatment cannot be affected directly by the treatments after the initial IVIG, there might exist confounders linking between the pre-IVIG HR and the post-IVIG status, which our decision for the additional treatments would be based on (eg, general appearance or other Kawasaki disease symptoms). The patients, who were considered at high risk of being IVIG nonresponders, or moreover developing CALs, may have been more likely to receive more aggressive treatment after the initial IVIG administration. Furthermore, the initial IVIG treatment itself might have been given at an earlier time. However, the proportion of those who received second IVIG or steroid treatment among groups 1 and 5 were almost the same (29% and 26%, respectively), and this was higher than the other groups (13%-17%). The timing of the initial IVIG administration was not recorded as being earlier in group 1. Therefore, the course of treatments could not sufficiently explain this result.

Third, the difference in inflammatory characteristics among patients might lead to this observation. Wang et al investigated whether Th1/Th2 cytokine profiles in children with Kawasaki disease were involved in IVIG resistance and development of CALs.²³ In this study, the pre-IVIG level of interleukin-6 was higher in patients with Kawasaki disease with CALs than those without CALs, while it was lower in IVIG nonresponders compared with IVIG responders. Diverse inflammatory cytokine profiles among patients with Kawasaki disease would lead to various clinical courses. Some patients might have persistent high fever without developing CALs, others could have

aggressive vasculitis even without high fever. However, information of patient's HR and body temperature would not be sufficient to differentiate them.

In Table 2, we found some differences in patients' characteristics between groups. The patients with the lowest $HRZ_{age/temp}$ (group 1) had higher percentage of neutrophil counts; whereas those with the highest $HRZ_{age/temp}$ (group 5) appeared to have higher platelet counts. One possible explanation is that the former might be patients who had greater systemic inflammation; the latter might be those with more aggressive vasculitis, which could be associated with diverse profiles of cytokines among patients. Further studies are needed to investigate the clinical utility of $HRZ_{age/temp}$ in patients with Kawasaki disease in consideration of other clinical presentations, or laboratory findings including cytokine profiles.

Exploratory plots of $HRZ_{age/temp}$ against age or body temperature suggested that there remained some association between HR and age even after adjustment using the formula reported by Daymont et al (Figure 4). Therefore, we also investigated the model including age as a covariate, but the result did not change. Other sensitivity analyses that showed the same trends strengthened the result.

There were several limitations to our study. First, there were several differences in the method between Daymont's study and our current study. We used axillary temperature, although core temperature was used in Daymont's study. The ethnicity of participants was also different. Second, because this was an observational study, there may have been unknown or unmeasured confounding variables. Patients' anxiety, discomfort, or pain may have increased HR. Use of antipyretics might have affected HR not only through decreasing body temperature but also reducing pain or discomfort. The body temperature might fluctuate depending on patient's sleep-awake cycle or environmental temperature. This study also included a relatively small sample size.

We only had 6.5 events per variable in the full model, which might not have yielded sufficient power to detect differences should they exist. There are also no scientifically plausible explanations for the relationship between the lower HR and the higher risk of IVIG responsiveness, or the conflicting result with respect to the development of CALs. Further studies are necessary to explore the association between autonomic nervous activity and clinical course of patients with Kawasaki disease with a theoretical basis for cytokines profiles.

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Figure 1: Flow chart of patient inclusion

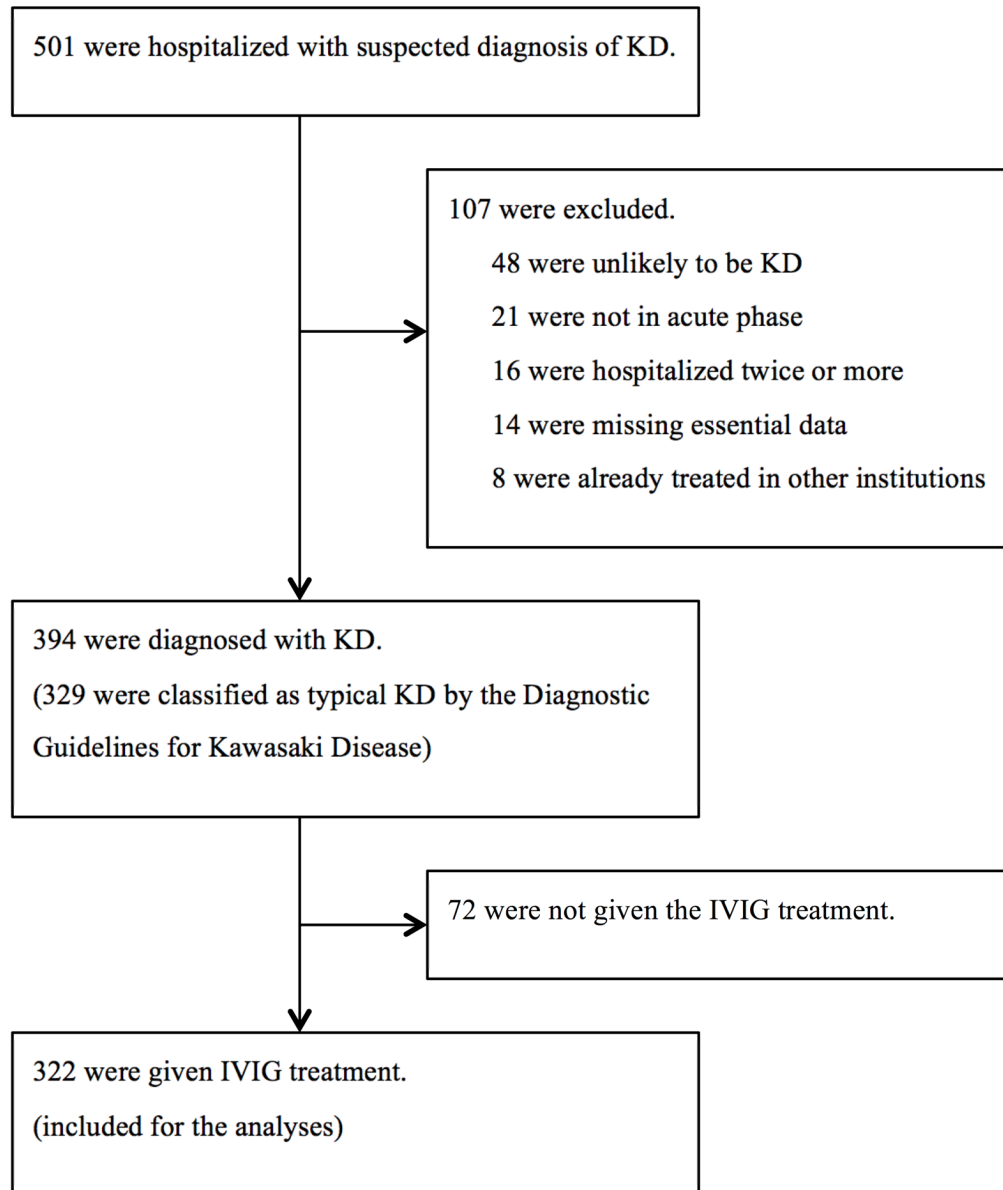


Figure 2: ORs of being refractory to initial IVIG treatment.

The points and bars indicate the estimates of ORs and 95% CIs. Patients were categorized into 5 groups according to $HRZ_{age/temp}$. Included covariates were as follows: model 1 (*squares*), only $HRZ_{age/temp}$ (*crude*); model 2 (*circles*), clinical day of the initial IVIG treatment, % neutrophil, PLT, CRP, sodium, and AST; model 3 (*triangles*), total bilirubin, hematocrit, and albumin as well as model 2; model 4, WBC, and sex as well as model 3.

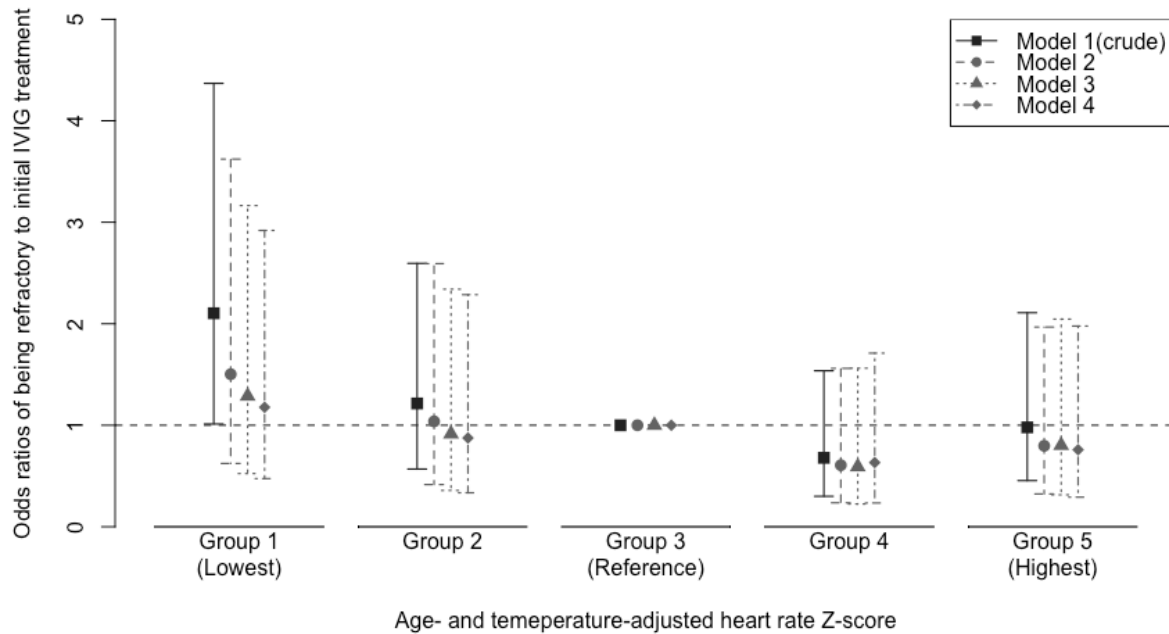


Figure 3: ORs of developing CALs.

The points and bars indicate the estimates of ORs and 95% CIs. Patients were categorized into 5 groups according to $HRZ_{age/temp}$. Included covariates were as follows: model 1 (*squares*), only $HRZ_{age/temp}$ (*crude*); model 2 (*circles*), clinical day of the initial IVIG treatment, % neutrophil, PLT, CRP, sodium, and AST; model 3 (*triangles*), total bilirubin, hematocrit and albumin as well as model 2; model 4, WBC and sex as well as model 3.

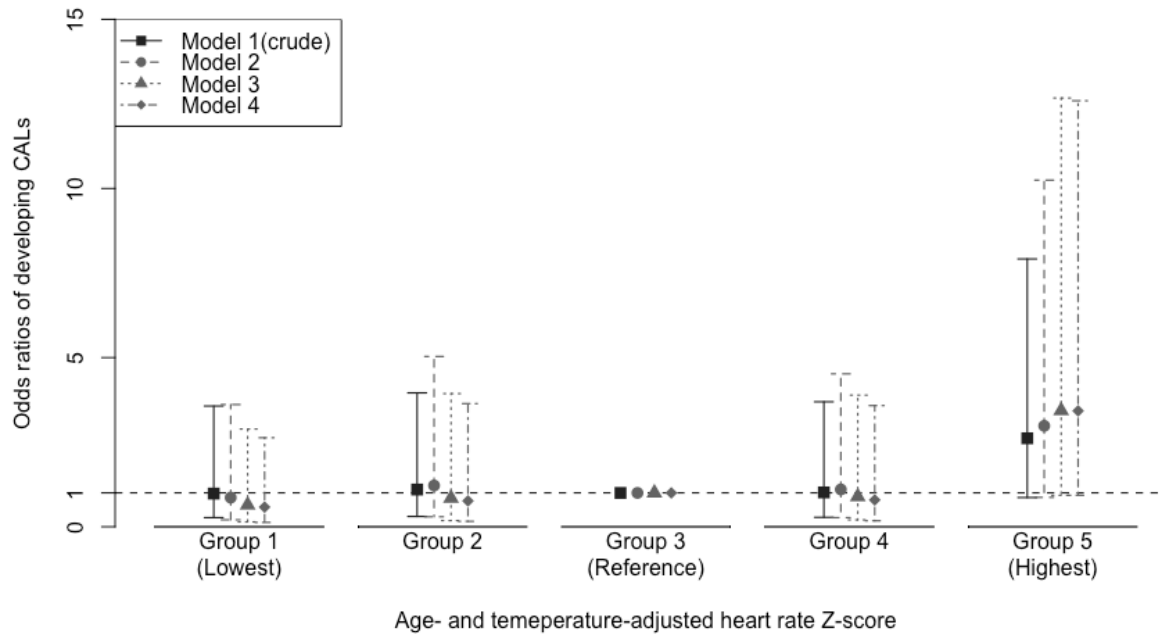


Figure 4(online only): Plots of $HRZ_{age/temp}$ against age and temperature.

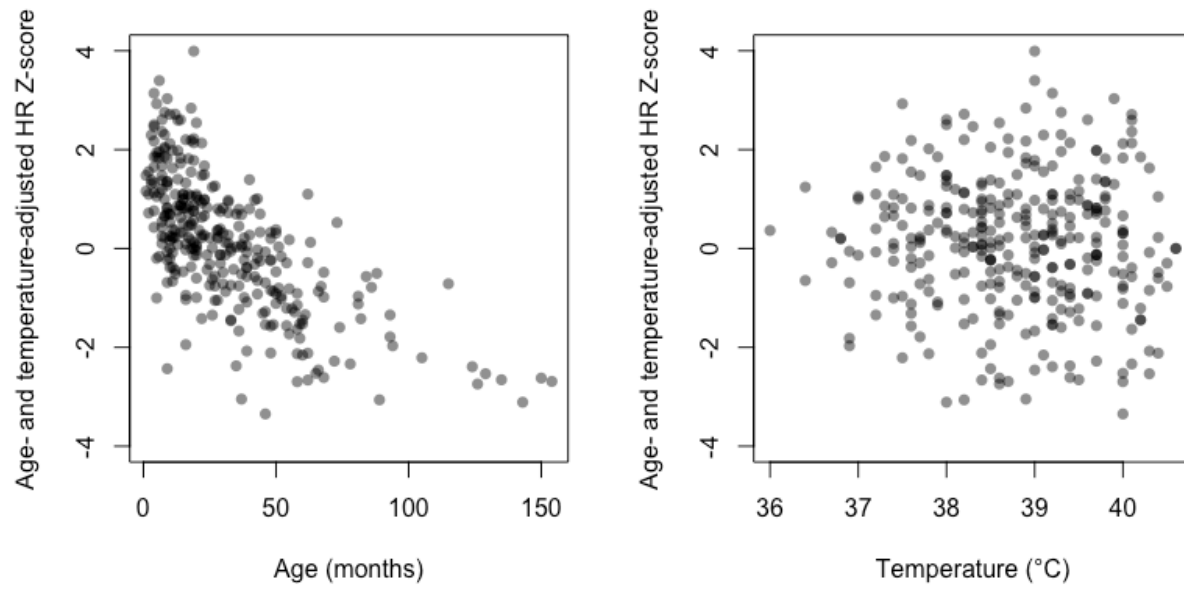


Table 1: Baseline characteristics of the patients who were responsive to initial IVIG treatment and those who were not.

	Responders (N=224)	Non-responders (N=98)	P-values
HRZ _{age/temp} , median (IQR)	0.26 (-0.52 to 1.01)	-0.10 (-1.29 to 0.80)	.006
Age, median (IQR), months	22 (11 to 39)	30 (16 to 53)	.01
Male sex, n (%)	129 (58%)	69 (70%)	.03
Clinical days of the initial IVIG treatment	5 (5 to 6)	5 (4 to 6)	.34
WBC, median (IQR), 10 ⁹ /L	12.9 (10.5 to 15.6)	12.7 (10.6 to 16.8)	.63
% Neutrophil, median (IQR), %	65 (51 to 76)	74 (63 to 83)	<.001
Hematocrit, median (IQR), %	33.6 (31.8 to 36.1)	34.3 (32.2 to 35.5)	.32
PLT, median (IQR), 10 ⁹ /L	336 (318 to 361)	313 (264 to 372)	.36
CRP, median (IQR), mg/dL	6.8 (4.4 to 9.9)	9.4 (6.0 to 14.0)	<.001
Serum sodium, median (IQR), mmol/L	135 (133 to 136)	133 (132 to 135)	.003
AST, median (IQR), U/L	34 (26 to 58)	38 (27 to 133)	.02
ALT, median (IQR), U/L	36 (15 to 102)	50 (15 to 165)	.05
Total bilirubin, median (IQR), md/dL	0.4 (0.3 to 0.6)	0.6 (0.4 to 1.0)	.004
Serum albumin, median (IQR), g/dL	3.5 (3.2 to 3.7)	3.4 (3.2 to 3.6)	.14
Duration of hospitalization, median (IQR), days	6 (5 to 7)	8 (7 to 12)	<.001
Second IVIG, n (%)	6 (3%)	59 (60%)	<.001
Steroid treatment, n (%)	1 (0.4%)	19 (19%)	<.001
Development of CALs, n(%)	15 (7%)	17 (17%)	.008

HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; IQR, interquartile range; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CAL, coronary artery lesion.

Table 2 (online only): Baseline characteristics of the patients according to age- and temperature-adjusted heart rate.

	Group 1	Group 2	Group 3	Group 4	Group 5
HRZ _{age/temp}	(-∞, -0.98)	[-0.98, -0.13)	[-0.13, 0.44)	[0.44, 1.12)	[1.12, +∞)
	n=65	n=63	n=65	n=63	n=66
Age, median (IQR), months	58 (39 to 72)	38 (22 to 50)	25 (14 to 35)	18 (13 to 26)	9 (5 to 16)
Male sex, n (%)	44 (68%)	36 (57%)	34 (52%)	44 (70%)	40 (61%)
Clinical days of the initial IVIG treatment	6 (4 to 6)	5 (4 to 6)	5 (4 to 6)	5 (4 to 6)	5 (4 to 6)
WBC, median (IQR), 10 ⁹ /L	13.3 (11.1 to 16.3)	12.7 (10.8 to 15.7)	12.5 (10.1 to 15.1)	14.3 (11.6 to 17.5)	12.4 (9.8 to 15.0)
% Neutrophil, median (IQR), %	80 (72 to 86)	74 (61 to 83)	63 (51 to 72)	60 (47 to 74)	62 (49 to 71)
Hematocrit, median (IQR), %	34.7 (32.8 to 36.7)	33.7 (32.0 to 36.1)	34.7 (32.2 to 36.3)	33.3 (31.5 to 35.0)	32.6 (30.5 to 34.8)
PLT, median (IQR), 10 ⁹ /L	302 (245 to 352)	313 (247 to 389)	328 (267 to 392)	327 (275 to 381)	334 (291 to 409)
CRP, median (IQR), mg/dL	8.6 (5.8 to 13.3)	7.2 (5.1 to 11.0)	6.8 (4.3 to 9.7)	7.2 (4.0 to 10.3)	7.9 (5.1 to 11.7)
Serum sodium, median (IQR), mmol/L	133 (132 to 135)	135 (133 to 137)	134 (132 to 136)	134 (133 to 135)	134 (133 to 136)
AST, median (IQR), U/L	33 (25 to 93)	36 (25 to 80)	38 (27 to 76)	35 (27 to 51)	34 (26 to 74)
ALT, median (IQR), U/L	34 (12 to 110)	52 (14 to 130)	46 (15 to 113)	30 (17 to 124)	45 (10 to 106)
Total bilirubin, median (IQR), md/dL	0.4 (0.3 to 0.6)	0.5 (0.4 to 0.7)	0.5 (0.3 to 0.7)	0.4 (0.3 to 0.7)	0.5 (0.4 to 0.7)
Serum albumin, median (IQR), g/dL	3.4 (3.1 to 3.6)	3.5 (3.2 to 3.6)	3.5 (3.3 to 3.8)	3.4 (3.2 to 3.6)	3.5 (3.3 to 3.7)
Duration of hospitalization, median (IQR), days	7 (6 to 10)	6 (5 to 7)	6 (5 to 8)	6 (5 to 7)	7 (5 to 8)
IVIG non-responders, n(%)	29 (45%)	20 (32%)	21 (32%)	17 (27%)	18 (27%)
Second IVIG, n (%)	19 (29%)	10 (16%)	11 (17%)	8 (13%)	17 (26%)
Steroid treatment, n (%)	8 (12%)	5 (8%)	2 (3%)	2 (3%)	3 (5%)
Development of CALs, n(%)	5 (8%)	5 (8%)	5 (8%)	5 (8%)	12 (18%)

HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase;

ALT, alanine aminotransferase; CAL, coronary artery lesion.

Table 3 (online only): Adjusted odds ratios of being refractory to initial IVIG treatment.

	Model 1	Model 2	Model 3	Model 4
HRZ _{age/temp}				
Group 1 (-∞, -0.98)	2.10 (1.01 to 4.37)	1.80 (0.80 to 4.04)	1.79 (0.79 to 4.04)	1.69 (0.74 to 3.85)
Group 2 [-0.98, -0.13)	1.21 (0.57 to 2.60)	1.26 (0.56 to 2.87)	1.21 (0.53 to 2.78)	1.20 (0.52 to 2.78)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	0.68 (0.30 to 1.54)	0.70 (0.30 to 1.67)	0.70 (0.29 to 1.68)	0.69 (0.28 to 1.68)
Group 5 [1.12, +∞)	0.98 (0.45 to 2.11)	0.90 (0.39 to 2.05)	0.92 (0.40 to 2.14)	0.91 (0.39 to 2.12)
Male sex	—	—	—	1.59 (0.91 to 2.78)
Clinical days of the initial IVIG treatment	—	0.96 (0.80 to 1.14)	0.97 (0.81 to 1.16)	0.97 (0.82 to 1.16)
WBC, 10 ⁹ /L	—	—	—	0.98 (0.91 to 1.05)
% Neutrophil, %	—	1.01 (0.99 to 1.03)	1.01 (0.98 to 1.03)	1.01 (0.98 to 1.03)
Hematocrit, %	—	—	1.01 (0.91 to 1.12)	1.02 (0.92 to 1.13)
PLT, 10 ⁹ /L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
CRP, mg/dL	—	1.05 (1.00 to 1.11)	1.05 (0.99 to 1.11)	1.06 (1.00 to 1.12)
Serum sodium, mmol/L	—	0.92 (0.83 to 1.02)	0.93 (0.83 to 1.03)	0.93 (0.84 to 1.04)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.26 (0.85 to 1.85)	1.24 (0.84 to 1.82)
Serum albumin, g/dL	—	—	0.83 (0.35 to 1.99)	0.90 (0.37 to 2.18)

HRZ_{age/temp} , Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 4 (online only): Adjusted odds ratios of developing CALs.

	Model 1	Model 2	Model 3	Model 4
HRZ _{age/temp}				
Group 1 ($-\infty$, -0.98)	0.98 (0.27 to 3.57)	0.86 (0.21 to 3.61)	0.64 (0.14 to 2.89)	0.58 (0.13 to 2.63)
Group 2 [-0.98, -0.13)	1.10 (0.30 to 3.96)	1.22 (0.29 to 5.03)	0.84 (0.18 to 3.94)	0.76 (0.16 to 3.64)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	1.01 (0.28 to 3.69)	1.10 (0.27 to 4.52)	0.89 (0.20 to 3.89)	0.79 (0.18 to 3.58)
Group 5 [1.12, $+\infty$)	2.61 (0.86 to 7.92)	2.98 (0.87 to 10.25)	3.43 (0.93 to 12.67)	3.43 (0.93 to 12.59)
Male sex	—	—	—	1.71 (0.65 to 4.51)
Clinical days of the initial IVIG treatment	—	1.19 (0.98 to 1.44)	1.15 (0.93 to 1.42)	1.16 (0.93 to 1.44)
WBC, $10^9/L$	—	—	—	1.02 (0.92 to 1.13)
% Neutrophil, %	—	1.00 (1.00 to 1.00)	0.99 (0.96 to 1.03)	0.99 (0.96 to 1.03)
Hematocrit, %	—	—	1.11 (0.95 to 1.30)	1.12 (0.95 to 1.32)
PLT, $10^9/L$	—	1.00 (1.00 to 1.01)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
CRP, mg/dL	—	1.06 (0.98 to 1.14)	1.03 (0.95 to 1.12)	1.02 (0.94 to 1.11)
Serum sodium, mmol/L	—	0.82 (0.71 to 0.96)	0.86 (0.73 to 1.01)	1.00 (1.00 to 1.00)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	0.86 (0.73 to 1.02)
Total bilirubin, mg/dL	—	—	1.63 (0.93 to 2.85)	1.62 (0.92 to 2.84)
Serum albumin, g/dL	—	—	0.09 (0.02 to 0.39)	0.09 (0.02 to 0.41)

CAL, coronary artery lesion; HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 5 (online only): HR corresponding to the quintile points of $HRZ_{age/temp}$.

Age	BT(°C)	Q1	Q2	Q3	Q4	Age	BT(°C)	Q1	Q2	Q3	Q4
3M	37.0	122	135	144	156	18M	37.0	107	120	130	142
	37.5	129	142	152	164		37.5	114	128	138	150
	38.0	136	150	159	171		38.0	121	135	145	157
	38.5	142	156	165	176		38.5	128	142	151	163
	39.0	148	161	170	181		39.0	133	147	157	168
	39.5	152	166	175	185		39.5	138	152	162	173
	40.0	156	170	179	190		40.0	142	157	166	178
6M	37.0	118	131	140	152	2Y	37.0	103	116	126	139
	37.5	125	138	148	160		37.5	110	124	134	147
	38.0	132	146	155	167		38.0	117	132	142	154
	38.5	138	152	161	172		38.5	124	138	148	161
	39.0	144	157	166	177		39.0	130	144	154	166
	39.5	148	162	171	182		39.5	135	149	159	171
	40.0	152	166	175	186		40.0	139	154	164	176
9M	37.0	115	128	137	149	3Y	37.0	97	111	121	134
	37.5	121	135	144	157		37.5	104	119	129	142
	38.0	129	142	152	163		38.0	112	127	137	150
	38.5	135	148	158	169		38.5	119	133	144	157
	39.0	140	154	163	174		39.0	124	139	150	162
	39.5	145	158	168	179		39.5	129	145	155	167
	40.0	149	163	172	183		40.0	134	149	160	172
12M	37.0	112	125	134	146	4Y	37.0	93	107	117	131
	37.5	118	132	142	154		37.5	100	115	126	139
	38.0	126	139	149	161		38.0	108	123	134	147
	38.5	132	146	155	167		38.5	115	130	141	154
	39.0	137	151	161	172		39.0	121	136	147	160
	39.5	142	156	165	176		39.5	126	142	152	165
	40.0	146	160	170	181		40.0	131	147	157	170

$HRZ_{age/temp}$, Z-score of HR adjusted for age and body temperatures; BT, body temperature; Q1 to Q5 are the quintile points which are the cutoff between Group1 and 2 to Group 4 and 5, respectively. The corresponding $HRZ_{age/temp}$ are -0.98, -0.13, 0.44 and 1.12, respectively.

Table 6 (online only): Adjusted odds ratios of being refractory to initial IVIG treatment (using the models in which age was added as covariates).

	Model 1 + age	Model 2 + age	Model 3 + age	Model 4 + age
HRZ _{age/temp}				
Group 1 (-∞, -0.98)	1.63 (0.71 to 3.76)	1.76 (0.72 to 4.28)	1.77 (0.72 to 4.36)	1.64 (0.66 to 4.07)
Group 2 [-0.98, -0.13)	1.11 (0.51 to 2.41)	1.26 (0.55 to 2.87)	1.20 (0.52 to 2.79)	1.19 (0.51 to 2.78)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	0.70 (0.31 to 1.60)	0.71 (0.30 to 1.67)	0.70 (0.29 to 1.68)	0.69 (0.28 to 1.67)
Group 5 [1.12, +∞)	1.09 (0.50 to 2.40)	0.91 (0.39 to 2.10)	0.93 (0.40 to 2.16)	0.92 (0.39 to 2.15)
Age, months	1.01 (1.00 to 1.02)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.02)
Male sex	—	—	—	1.60 (0.91 to 2.79)
Clinical days of the initial IVIG treatment	—	0.95 (0.80 to 1.14)	0.97 (0.81 to 1.16)	0.97 (0.81 to 1.16)
WBC, 10 ⁹ /L	—	—	—	0.98 (0.91 to 1.05)
% Neutrophil, %	—	1.01 (0.98 to 1.03)	1.01 (0.98 to 1.03)	1.01 (0.98 to 1.03)
Hematocrit, %	—	—	1.01 (0.91 to 1.12)	1.02 (0.92 to 1.13)
PLT, 10 ⁹ /L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
CRP, mg/dL	—	1.05 (1.00 to 1.11)	1.05 (0.99 to 1.11)	1.06 (1.00 to 1.12)
Serum sodium, mmol/L	—	0.92 (0.83 to 1.02)	0.93 (0.83 to 1.03)	0.93 (0.84 to 1.82)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.26 (0.85 to 1.85)	1.24 (0.84 to 1.82)
Serum albumin, g/dL	—	—	0.83 (0.35 to 1.99)	0.90 (0.37 to 2.19)

HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 7 (online only): Adjusted odds ratios of developing CALs (using the models in which age was added as covariates).

	Model 1 + age	Model 2 + age	Model 3 + age	Model 4 + age
HRZ _{age/temp}				
Group 1 (-∞, -0.98)	0.68 (0.15 to 3.10)	0.82 (0.16 to 4.13)	0.66 (0.11 to 3.83)	0.60 (0.10 to 3.53)
Group 2 [-0.98, -0.13)	0.97 (0.26 to 3.58)	1.20 (0.29 to 5.06)	0.85 (0.18 to 4.12)	0.77 (0.16 to 3.80)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	1.06 (0.29 to 3.89)	1.11 (0.27 to 4.54)	0.89 (0.20 to 3.89)	0.79 (0.17 to 3.58)
Group 5 [1.12, +∞)	3.02 (0.96 to 9.49)	3.04 (0.86 to 10.76)	3.41 (0.91 to 12.77)	3.41 (0.92 to 12.66)
Age, months	1.01 (0.99 to 1.03)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
Male sex	—	—	—	1.71 (0.65 to 4.52)
Clinical days of the initial IVIG treatment	—	1.19 (0.98 to 1.44)	1.15 (0.92 to 1.43)	1.16 (0.93 to 1.46)
WBC, 10 ⁹ /L	—	—	—	1.02 (0.92 to 1.13)
% Neutrophil, %	—	1.00 (0.97 to 1.04)	0.99 (0.96 to 1.03)	0.99 (0.96 to 1.03)
Hematocrit, %	—	—	1.11 (0.94 to 1.31)	1.12 (0.95 to 1.33)
PLT, 10 ⁹ /L	—	1.00 (1.00 to 1.01)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
CRP, mg/dL	—	1.06 (0.98 to 1.14)	1.03 (0.95 to 1.12)	1.03 (0.94 to 1.12)
Serum sodium, mmol/L	—	0.82 (0.71 to 0.96)	0.86 (0.73 to 1.01)	0.86 (0.73 to 1.02)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.63 (0.93 to 2.85)	1.62 (0.92 to 2.84)
Serum albumin, g/dL	—	—	0.09 (0.02 to 0.40)	0.09 (0.02 to 0.41)

CAL, coronary artery lesion; HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 8 (online only): Adjusted odds ratios of being refractory to initial IVIG treatment (using only the data of typical KD).

	Model 1	Model 2	Model 3	Model 4
HRZ _{age/temp}				
Group 1 (-∞, -0.98)	2.27 (1.02 to 5.08)	1.86 (0.77 to 4.51)	1.88 (0.77 to 4.57)	1.84 (0.75 to 4.50)
Group 2 [-0.98, -0.13)	1.51 (0.67 to 3.40)	1.50 (0.63 to 3.60)	1.50 (0.62 to 3.64)	1.49 (0.61 to 3.64)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	0.78 (0.33 to 1.86)	0.84 (0.33 to 2.11)	0.88 (0.35 to 2.23)	0.89 (0.34 to 2.30)
Group 5 [1.12, +∞)	1.02 (0.45 to 2.31)	0.97 (0.40 to 2.34)	1.04 (0.42 to 2.59)	1.01 (0.41 to 2.53)
Male sex	—	—	—	1.23 (0.68 to 2.22)
Clinical days of the initial IVIG treatment	—	0.93 (0.76 to 1.12)	0.94 (0.77 to 1.15)	0.95 (0.78 to 1.16)
WBC, 10 ⁹ /L	—	—	—	0.98 (0.90 to 1.06)
% Neutrophil, %	—	1.01 (0.99 to 1.04)	1.01 (0.99 to 1.04)	1.01 (0.99 to 1.04)
Hematocrit, %	—	—	1.04 (0.93 to 1.16)	1.04 (0.93 to 1.17)
PLT, 10 ⁹ /L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
CRP, mg/dL	—	1.05 (0.99 to 1.11)	1.05 (0.99 to 1.11)	1.06 (1.00 to 1.12)
Serum sodium, mmol/L	—	0.93 (0.83 to 1.03)	0.93 (0.83 to 1.04)	0.93 (0.83 to 1.04)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.13 (0.76 to 1.68)	1.13 (0.76 to 1.67)
Serum albumin, g/dL	—	—	0.98 (0.39 to 2.48)	1.04 (0.40 to 2.68)

HRZ_{age/temp} , Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 9 (online only): Adjusted odds ratios of developing CALs (using only the data of typical KD).

	Model 1	Model 2	Model 3	Model 4
HRZ _{age/temp}				
Group 1 (-∞, -0.98)	1.04 (0.28 to 3.81)	0.91 (0.22 to 3.79)	0.67 (0.15 to 3.06)	0.61 (0.13 to 2.78)
Group 2 [-0.98, -0.13)	1.15 (0.33 to 4.04)	1.22 (0.30 to 4.91)	0.81 (0.18 to 3.71)	0.73 (0.16 to 3.40)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	0.96 (0.26 to 3.50)	1.07 (0.26 to 4.40)	0.83 (0.19 to 3.66)	0.73 (0.16 to 3.34)
Group 5 [1.12, +∞)	2.40 (0.79 to 7.27)	2.73 (0.79 to 9.37)	2.81 (0.74 to 10.64)	2.74 (0.73 to 10.33)
Male sex	—	—	—	1.65 (0.62 to 4.37)
Clinical days of the initial IVIG treatment	—	1.18 (0.98 to 1.42)	1.13 (0.92 to 1.40)	1.15 (0.92 to 1.43)
WBC, 10 ⁹ /L	—	—	—	1.02 (0.92 to 1.13)
% Neutrophil, %	—	1.01 (0.97 to 1.04)	0.99 (0.95 to 1.02)	0.99 (0.95 to 1.03)
Hematocrit, %	—	—	1.08 (0.92 to 1.27)	1.09 (0.92 to 1.29)
PLT, 10 ⁹ /L	—	1.00 (1.00 to 1.00)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
CRP, mg/dL	—	1.06 (0.98 to 1.14)	1.04 (0.95 to 1.12)	1.03 (0.95 to 1.12)
Serum sodium, mmol/L	—	0.84 (0.72 to 0.97)	0.87 (0.74 to 1.03)	0.88 (0.74 to 1.03)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.77 (1.06 to 2.96)	1.75 (1.04 to 2.93)
Serum albumin, g/dL	—	—	0.09 (0.02 to 0.44)	0.09 (0.02 to 0.44)

CAL, coronary artery lesion; HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 10 (online only): Adjusted odds ratios of being refractory to initial IVIG treatment (using only the data without missings).

	Model 1	Model 2	Model 3	Model 4
HRZ _{age/temp}				
Group 1 ($-\infty$, -0.98)	2.10 (1.01 to 4.37)	1.50 (0.62 to 3.62)	1.29 (0.52 to 3.16)	1.18 (0.47 to 2.92)
Group 2 [-0.98, -0.13)	1.21 (0.57 to 2.60)	1.04 (0.42 to 2.59)	0.91 (0.36 to 2.34)	0.87 (0.33 to 2.29)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	0.68 (0.30 to 1.54)	0.61 (0.24 to 1.56)	0.59 (0.22 to 1.56)	0.63 (0.23 to 1.71)
Group 5 [1.12, $+\infty$)	0.98 (0.45 to 2.11)	0.80 (0.32 to 1.97)	0.80 (0.31 to 2.05)	0.76 (0.29 to 1.98)
Male sex	—	—	—	1.84 (0.96 to 3.53)
Clinical days of the initial IVIG treatment	—	1.02 (0.86 to 1.20)	1.06 (0.89 to 1.27)	1.07 (0.90 to 1.28)
WBC, $10^9/L$	—	—	—	0.94 (0.86 to 1.02)
% Neutrophil, %	—	1.01 (0.99 to 1.04)	1.01 (0.99 to 1.04)	1.02 (0.99 to 1.04)
Hematocrit, %	—	—	1.03 (0.92 to 1.15)	1.05 (0.93 to 1.18)
PLT, $10^9/L$	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
CRP, mg/dL	—	1.03 (0.97 to 1.09)	1.05 (0.99 to 1.11)	1.06 (0.99 to 1.13)
Serum sodium, mmol/L	—	0.90 (0.81 to 1.01)	0.91 (0.81 to 1.03)	0.91 (0.81 to 1.03)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.38 (0.89 to 2.14)	1.38 (0.89 to 2.14)
Serum albumin, g/dL	—	—	1.07 (0.39 to 2.92)	1.28 (0.45 to 3.63)

HRZ_{age/temp} , Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.

Table 11 (online only): Adjusted odds ratios of developing CALs (using only the data without missings).

	Model 1	Model 2	Model 3	Model 4
HRZ _{age/temp}				
Group 1 (-∞, -0.98)	0.98 (0.27 to 3.57)	0.73 (0.16 to 3.37)	0.47 (0.09 to 2.46)	0.42 (0.08 to 2.24)
Group 2 [-0.98, -0.13)	1.04 (0.28 to 3.77)	1.39 (0.31 to 6.15)	0.99 (0.20 to 4.88)	0.85 (0.16 to 4.34)
Group 3 [-0.13, 0.44)	reference	reference	reference	reference
Group 4 [0.44, 1.12)	1.02 (0.28 to 3.70)	1.24 (0.30 to 5.20)	0.80 (0.18 to 3.62)	0.67 (0.14 to 3.20)
Group 5 [1.12, +∞)	2.62 (0.87 to 7.93)	3.14 (0.86 to 11.44)	2.82 (0.71 to 11.26)	2.93 (0.73 to 11.72)
Male sex	—	—	—	2.06 (0.71 to 6.00)
Clinical days of the initial IVIG treatment	—	1.19 (0.98 to 1.46)	1.13 (0.90 to 1.41)	1.14 (0.91 to 1.44)
WBC, 10 ⁹ /L	—	—	—	1.04 (0.93 to 1.15)
% Neutrophil, %	—	1.01 (0.97 to 1.04)	0.99 (0.96 to 1.03)	0.99 (0.96 to 1.03)
Hematocrit, %	—	—	1.09 (0.93 to 1.29)	1.11 (0.93 to 1.31)
PLT, 10 ⁹ /L	—	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
CRP, mg/dL	—	0.83 (0.70 to 0.98)	1.03 (0.94 to 1.12)	1.02 (0.92 to 1.12)
Serum sodium, mmol/L	—	0.83 (0.70 to 0.98)	0.89 (0.74 to 1.07)	0.90 (0.75 to 1.08)
AST, U/L	—	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Total bilirubin, mg/dL	—	—	1.83 (0.95 to 3.51)	1.85 (0.96 to 3.57)
Serum albumin, g/dL	—	—	0.08 (0.02 to 0.42)	0.08 (0.02 to 0.40)

CAL, coronary artery lesion; HRZ_{age/temp}, Z-score of HR adjusted for age and body temperatures; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; AST, aspartate aminotransferase.