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Impact of 10% vs. 5% immunoglobulin products on treatment outcomes in Kawasaki disease: a multicenter retrospective study

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Kawasaki disease (KD) is an acute vasculitis predominantly affecting younger children, and intravenous immunoglobulin (IVIG) treatment can reduce coronary artery lesion (CAL) development. This multicenter retrospective study aimed to evaluate whether using 10% immunoglobulin products, which allow for faster IVIG administration than conventional 5% immunoglobulin products, impact KD treatment outcomes. We analyzed data of 496 patients with KD from nine Japanese hospitals, divided into 5% ($n = 247$) and 10% ($n = 249$) immunoglobulin groups. The results show that the 10% immunoglobulin group had a shorter duration of IVIG infusion compared to the 5% group (12.9 vs. 24.3 h, $P < 0.001$) but had a lower cumulative incidence of fever resolution 24 h after starting IVIG (66.7% vs. 77.7%, $P = 0.023$), and the difference was maintained thereafter. The 10% group also had more IVIG nonresponders (24% vs. 17%, $P = 0.046$). There were no significant differences in the interval between primary and secondary treatment or in the incidence of CALs and severe adverse events. These findings suggest that while 10% immunoglobulin products facilitate faster IVIG administration, they may lead to increased nonresponse rates, highlighting the need for further studies to optimize KD treatment protocols, such as duration of IVIG administration.

Keywords Children, Coronary artery lesion, Immunoglobulin products concentration, Immunoglobulin-related adverse event, Intravenous Immunoglobulin, Kawasaki disease

Kawasaki disease (KD) is an acute vasculitis of unknown cause predominantly affecting younger children and is a major cause of acquired heart disease in children, especially in developed countries, as coronary artery lesions (CALs) occur in approximately 25% of untreated cases[1]. Intravenous immunoglobulin (IVIG) administration in the acute phase of KD has been reported to significantly reduce CAL development[2,3], and 2 g/kg of IVIG in a single continuous infusion together with aspirin is the recommended primary treatment for KD[1,4].

In Japan, all available immunoglobulin have been 5% products previously; however, 10% immunoglobulin products are now being used more frequently for treating KD since its launch in 2013. Owing to the difference in concentration, 10% immunoglobulin products can be administered faster and with a smaller volume for the same dose of immunoglobulin than 5% immunoglobulin products.

Considering that reducing inflammation earlier and preventing CAL development are the goals of treatment in the acute phase of KD[1], we hypothesized that the use of 10% immunoglobulin products that allow for faster IVIG administration can result in rapid fever resolution in patients and consequently decrease CAL incidence.

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There have been few studies comparing differences in the concentrations of immunoglobulin products for the treatment of the acute phase of KD, all of which have been conducted at single centers[5–7].

Therefore, we conducted a multicenter study to assess the impact of immunoglobulin product concentration on the efficacy and safety of treatment in the acute phase of KD.

Results

Patient characteristics

A total of 524 patients were initially enrolled from nine Japanese hospitals. We excluded four transferred patients, one patient who was misdiagnosed, eight patients who received a primary IVIG dose outside the range of 1.5–2.5 g/kg, 14 patients who had already resolved fever at the start of primary IVIG administration, and one patient with missing data on fever resolution time. Consequently, the final cohort included 496 patients, with 247 and 249 in the 5% and 10% immunoglobulin groups, respectively (Supplementary Fig. S1A).

The clinical and laboratory characteristics of 496 patients are summarized in Table 1. No significant differences were observed between the two groups except for a higher number of patients with incomplete KD and lower sodium levels in the 10% immunoglobulin group than those in the 5% immunoglobulin group. The Kobayashi score[8] and duration of fever onset to start treatment did not differ between the two groups.

Primary treatment details and responses

The duration of IVIG infusion in the primary treatment was significantly shorter in the 10% immunoglobulin group compared to 5% immunoglobulin group (12.9 h vs. 24.3 h, $P<0.001$) (Fig. 1A and Table 2). No difference was noted between the two groups in the IVIG dose for primary treatment or in the number of patients treated with concurrent steroids (Table 2). Regarding the administered immunoglobulin products, in the 5% immunoglobulin group, 239 patients received Venoglobulin IH (Japan Blood Products Organization, Tokyo, Japan), and the remaining 8 patients received Polyglobin N (Japan Blood Products Organization). In the 10% immunoglobulin group, all patients received Venoglobulin IH (Japan Blood Products Organization).

The 10% immunoglobulin group had a significantly higher number of nonresponders to primary treatment (61 [24.5%] vs. 42 [17.0%], $P=0.046$). No significant difference in the number of relapsed patients or those who required secondary treatment was observed between the two groups. In nonresponders to primary treatment,

	5% immunoglobulin group	10% immunoglobulin group	
	N = 247	*N* = 249	*P* value
Demographics			
Age at diagnosis, month	27 (0–156)	27 (1–150)	0.38
Sex, male, n	144 (58.3%)	133 (53.4%)	0.28
Body weight at diagnosis, kg	12.0 (3.5–42.1)	12.0 (4.5–50.0)	0.61
Diagnosis, incomplete Kawasaki disease, n	19 (7.7%)	35 (14.1%)	0.03
Kobayashi score*	4 (0–10)	3 (0–10)	0.38
Delay fever onset-treatment, day	5 (2–9)	5 (2–9)	0.61
Clinical symptoms of Kawasaki disease			
Fever, n	247 (100.0%)	249 (100.0%)	–
Bilateral bulbar conjunctival injection, n	231 (93.5%)	220 (88.4%)	0.06
Changes of lips and oral cavity, n	228 (92.3%)	224 (90.0%)	0.43
Rash, n	223 (90.3%)	222 (89.2%)	0.77
Changes of peripheral extremities, n	220 (89.1%)	209 (83.9%)	0.12
Non-supparative cervical lymphadenopathy, n	198 (80.2%)	189 (75.9%)	0.28
Laboratory findings			
White blood cell count, 10^9/L	13.4 (4.8–35.5)	14.6 (2.8–36.7)	0.20
Neutrophil cells, %	73.0 (12.5–95.0)	71.7 (23.0–95.0)	0.49
Hemoglobin*, g/L	114 (74–142)	114 (65–137)	0.95
Hematocrit, %	34.0 (23.1–55.0)	33.8 (22.6–41.0)	0.36
Platelet count, 10^9/L	323 (122–743)	336 (71–640)	0.26
C-reactive protein, mg/L	73.1 (1.0–307.1)	73.8 (1.7–284.5)	0.81
Total protein†, g/L	66 (48–79)	66 (47–84)	0.95
Albumin, g/L	35 (19–46)	35 (23–45)	0.33
Aspartate transaminase, U/L	39 (16–2000)	41 (19–1909)	0.40
Alanine transaminase, U/L	23 (3–1117)	28 (6–1011)	0.14
Sodium*, mmol/L	134 (126–141)	134 (125–142)	0.01

Table 1. Baseline patient characteristics. Continuous variables: median and range. *One patient in the 10% immunoglobulin group had no data available. †One patient in the 5% immunoglobulin group and one patient in the 10% immunoglobulin group had no data available.

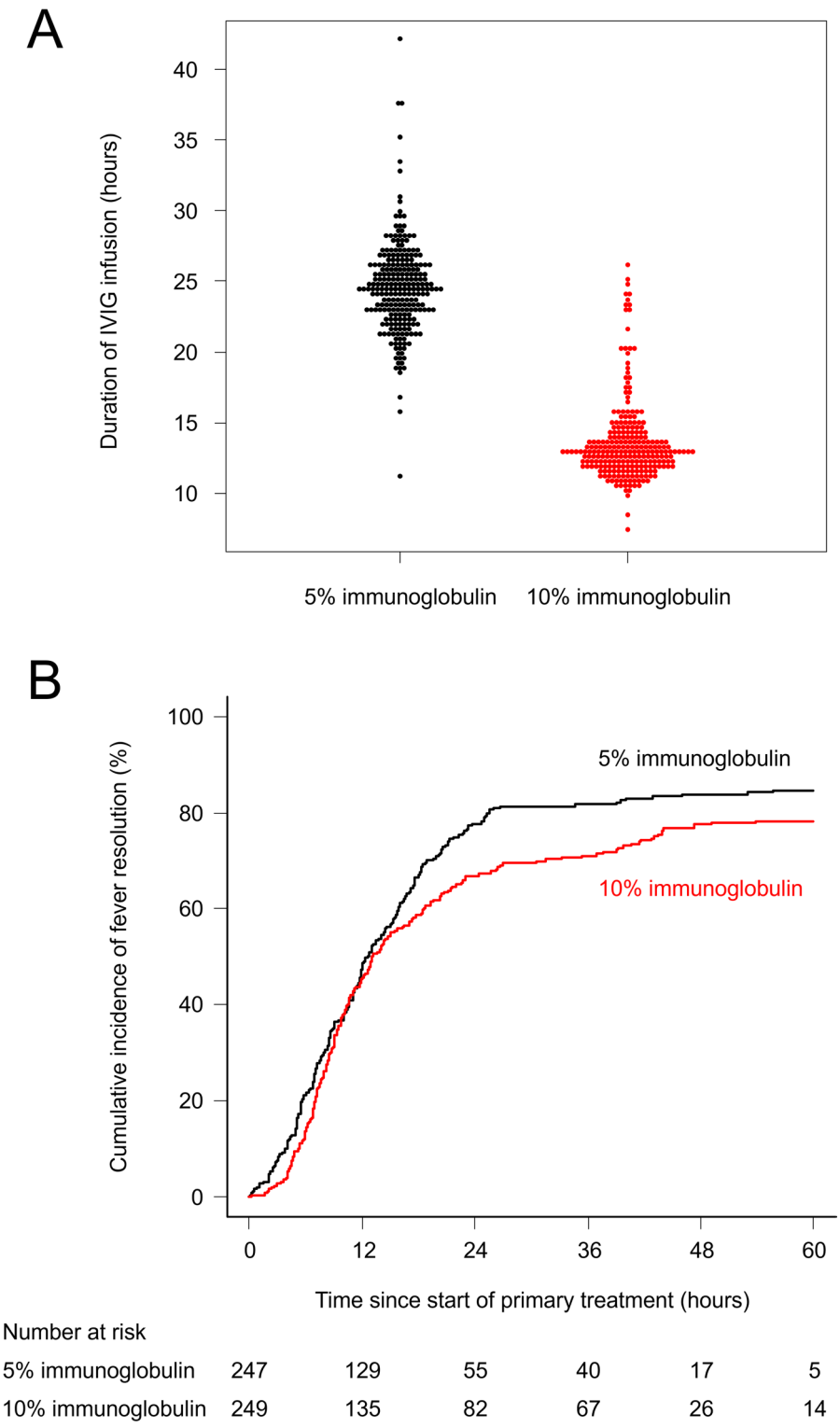

Fig. 1. (**A**) Duration of IVIG infusion. Each dot represents one patient. (**B**) Cumulative incidence of fever resolution after the start of primary treatment, estimated using the competing risks method, with the start of secondary treatment considered a competing event. The black line represents the cumulative incidence of fever resolution in the 5% immunoglobulin group, whereas the red line represents that in the 10% immunoglobulin group.

	5% immunoglobulin group	10% immunoglobulin group	
	N = 247	*N* = 249	*P* value
Primary treatment			
Duration of IVIG infusion*, hour	24.3 (11.0–42.2)	12.9 (7.5–25.9)	< 0.001
Dose of IVIG infusion, g/kg	2.0 (1.5–2.3)	2.0 (1.6–2.5)	0.79
Steroid use with IVIG, n	35 (14.2%)	27 (10.8%)	0.28
Clinical outcomes			
Nonresponders to primary treatment, n	42 (17.0%)	61 (24.5%)	0.046
Relapse, n	31 (12.6%)	24 (9.6%)	0.32
Requirement of the secondary treatment, n	69 (27.9%)	77 (30.9%)	0.49
Interval between primary and secondary treatment†, hour	46.9 (24.2–68.8)	46.4 (12.8–92.4)	0.54
CAL within 28 days after primary treatment, n	15 (6.1%)	27 (10.8%)	0.08
CAL at 28 days after primary treatment, n	6 (2.4%)	6 (2.4%)	> 0.99
Hospital stay‡, day	11 (5–35)	11 (4–55)	0.25
Adverse events of IVIG infusion			
Severe adverse event, n	1 (0.4%)	0 (0.0%)	0.50
Extravasation during IVIG infusion, n	9 (3.6%)	13 (5.2%)	0.51

Table 2. Treatment, clinical outcomes, and adverse events in the two treatment groups. Continuous variables: median and range. *Two patients in the 5% immunoglobulin group and one patient in the 10% immunoglobulin group had no data available. †Compared in 97 nonresponders to primary treatment, who required secondary treatment. ‡Five patients in the 10% immunoglobulin group who were transferred to a higher order medical institution due to poor response to treatment had no data available. CAL, coronary artery lesion; IVIG, intravenous immunoglobulin.

	Univariable		Multivariable	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at diagnosis				
< 12 months old	1		–	
≥ 12 months old	1.08 (0.61–1.90)	0.80	–	–
Sex				
Male	1		–	
Female	1.31 (0.85–2.03)	0.22	–	–
Disease				
Incomplete KD	1		–	
KD	1.86 (0.81–4.25)	0.14	–	–
Kobayashi score				
< 5 points	1		1	
≥ 5 points	2.05 (1.32–3.18)	0.001	3.08 (1.93–4.93)	< 0.001
Concentration of immunoglobulin				
5%	1		1	
10%	1.58 (1.02–2.46)	0.04	1.63 (1.03–2.58)	0.04
Steroid use with IVIG				
Yes	1		1	
No	5.89 (1.81–19.2)	0.003	10.6 (3.15–35.6)	< 0.001

Table 3. Univariable and multivariable analyses of risk factors associated with nonresponse to primary treatment. CI, confidence intervals; OR, odds ratio; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

the interval between the start of primary and secondary treatments did not differ between the two groups (46.4 h vs. 46.9 h, $P < 0.54$) (Table 2).

Table 3 shows the results of univariate and multivariate analyses of risk factors associated with nonresponse to primary treatment. In the univariate analysis, the risk factors for nonresponse to primary treatment included a Kobayashi score of ≥ 5 points, the absence of steroid use combined with IVIG, and the use of 10% immunoglobulin products. The multivariate analysis showed that the immunoglobulin product concentration (5% or 10%) was a risk factor for nonresponse to primary treatment, which was independent of the Kobayashi score and steroid use combined with IVIG.

Fever duration analysis

The cumulative incidence of fever resolution since the start of the primary IVIG administration is shown in Fig. 1B and Supplementary Table S1. At 12 h after the start of primary IVIG administration, no difference in the cumulative incidence of fever resolution between the 10% and 5% immunoglobulin groups were noted (45.8% [95% confidence interval {CI}: 39.5–51.9%] vs. 48.6% [95% CI: 42.2–54.7%], $P = 0.414$). However, at 24 h, the cumulative incidence of fever resolution significantly differed between the two groups (66.7% [95% CI: 60.4–72.2%] vs. 77.7% [95% CI: 72.0–82.5%], $P = 0.023$), and the difference was maintained thereafter.

Outcomes and adverse events

The overall clinical course including the details of the secondary treatment is summarized in Supplementary Fig. S2. The overall incidence of CALs and their size classification based on Z-scores are summarized in Table 2 and Supplementary Table S2. The frequency of CALs within 28 days of primary treatment was approximately twice as high in the 10% immunoglobulin group as that in the 5% immunoglobulin group; however, this difference was not statistically significant (27 [10.8%] vs. 15 [6.1%], $P = 0.075$). The hospitalization duration did not differ between the two groups.

Only one severe adverse event (AE) was noted in the 5% immunoglobulin group (anaphylaxis occurred immediately after the end of IVIG administration); no difference in the incidence of severe AEs was observed between the two groups. The frequency of extravasation during primary IVIG infusion was also similar between the two groups.

Subgroup analysis of patients treated without concurrent steroids

To address the potential confounding effect of steroids on fever resolution, a subgroup analysis was performed including only patients who did not receive concurrent steroids ($n = 434$; 10% immunoglobulin group: $n = 222$, 5% immunoglobulin group: $n = 212$). Among these patients, the number of nonresponders to primary treatment was 59 (26.6%) in the 10% immunoglobulin group and 41 (19.3%) in the 5% immunoglobulin group. The results of the univariate and multivariate analyses of factors associated with nonresponse to primary treatment are shown in Supplementary Table S3. While the use of 10% immunoglobulin was not statistically significant in univariate analysis, it was identified as an independent risk factor in multivariate analysis adjusted for the Kobayashi score (odds ratio: 1.61 [95% CI: 1.01–2.58], $P = 0.04$).

The cumulative incidence of fever resolution from the start of primary IVIG administration is shown in Supplementary Fig. S3 and Supplementary Table S4. Consistent with the overall cohort, there was no difference between groups at 12 h; however, at 24 h, the 5% group showed a significantly higher incidence of fever resolution.

Discussion

In this study, we investigated whether differences in immunoglobulin product concentrations affect the efficacy and safety of acute phase treatment for KD. The use of 10% immunoglobulin products significantly reduced the IVIG infusion duration compared with the use of 5% immunoglobulin products. However, the cumulative incidence of fever resolution 24 h after of starting IVIG administration was lower and the number of nonresponders to primary IVIG treatment was higher in the 10% immunoglobulin group. The interval between the start of primary and secondary treatment was not shortened using the 10% immunoglobulin product. The immunoglobulin concentration did not affect CAL or AE occurrence.

There have been two single-center retrospective studies conducted in Japan comparing 10% and 5% immunoglobulin products in the acute phase treatment of KD, and both studies reported that immunoglobulin product concentration was not associated with the response to primary IVIG treatment[5]. Meanwhile, a recent study conducted in Korea showed an increase in primary IVIG treatment failure with the use of 10% immunoglobulin products compared with that of 5% immunoglobulin products[7]. Furthermore, Suzuki et al. recently published a large-scale study comparing 10% and 5% immunoglobulin products using the Diagnosis Procedure Combination database of Japan, which showed a significant association between the use of 10% immunoglobulin products and an increase in primary IVIG treatment failure[9]. The current multicenter study reported that the use of 10% immunoglobulin products increased the number of nonresponders to primary IVIG treatment compared with that of 5% immunoglobulin products.

The immunoglobulin products used in our study did not differ in characteristics other than immunoglobulin concentration, including osmotic pressure or sodium content, and it is unlikely that these factors influenced treatment efficacy. As shown in Fig. 1B, the difference in the cumulative incidence of fever resolution between the 10% and 5% immunoglobulin group at 12 to 24 h after the start of primary IVIG administration suggests that the IVIG administration duration can be implicated in the increase in primary IVIG treatment failure in the 10% immunoglobulin group. It has been reported that low peak serum immunoglobulin G (IgG) levels following primary IVIG administration are associated with poor IVIG treatment response[10,11]. Additionally, Fukui et al. reported that serum IgG levels on the second day after the start of primary IVIG administration significantly increased from baseline in patients who received 24-hour IVIG compared with those who received 12-hour IVIG infusion[12]. Considering these studies, it may be possible that in the 10% immunoglobulin group, rapid IVIG administration during the "very" acute phase of KD, when inflammation was strong and vascular permeability was increased, resulted in increased extravascular distribution of IgG, decreased peak serum IgG levels, and thus increased the number of nonresponders to primary IVIG treatment compared with the 5% immunoglobulin group. Owing to the retrospective nature of this study, we could not collect clinical laboratory data, including serum IgG levels, at specific time points following treatment. To validate this hypothesis, we are conducting a prospective study comparing the speed of IVIG administration (jRCT1041230181).

In the current study, the interval between the start of primary and secondary treatments in IVIG nonresponders was not shortened using the 10% immunoglobulin product, which differed from the results of previous studies[5,6].

In Japanese guidelines for the acute phase treatment of KD, evaluating the response to IVIG at 48 h after the start of primary IVIG administration is recommended[4]. However, in clinical practice, we occasionally proceed to secondary treatment before the 48-hour mark on the basis of the patient's condition, and this decision is greatly influenced by the institution's policy. This difference in clinical practice may explain the discrepancy between the results of the current study and those of previous studies regarding whether the interval between the start of primary and secondary treatment in IVIG nonresponders was shortened using the 10% immunoglobulin product or not. A shorter IVIG administration duration allows for an earlier secondary treatment initiation, which is particularly beneficial in high-risk patients with IVIG nonresponse, thereby enabling more aggressive additional treatments. However, there is also the potential for overtreatment in patients who may not actually require secondary treatment. Therefore, careful evaluation is necessary to create an appropriate balance between prompt intervention for at-risk patients and avoiding unnecessary treatment for patients who respond well to IVIG alone.

Consistent with previous studies[5–7,9], no difference was observed in the incidence of CALs based on the immunoglobulin product concentration used in the present study. Considering the low CAL incidence, the number of patients in our study was insufficient to fully evaluate the incidence of CALs, and a larger study would be needed to validate this finding.

In the current study, the incidence of severe AEs was not different between the 10% and 5% immunoglobulin products. Although the small number of severe AEs may limit the strength of the conclusion, it is presumed that the 10% immunoglobulin product is as safe as the 5% immunoglobulin product in the acute phase treatment of KD.

This study had several limitations. First, the limited number of patients in the retrospective design may have prevented a thorough assessment of the causal relationship between IVIG product concentration and treatment outcomes. However, this study is unique among similar studies in that it was conducted across multiple institutions and included a substantial number of cases, and its findings provide crucial insights into understanding the impact of immunoglobulin product concentration on the acute phase treatment of KD.

Second, axillary temperature was used to assess fever resolution, which may be less reliable than core temperature measurements. However, this method is widely used in clinical practice in Japan and is consistent with the current Japanese guidelines for evaluating treatment response in KD[4].

Third, the generalizability of our findings to countries outside Japan may be limited. For example, in the United States, IVIG is typically infused over 10–12 h, and the average duration of hospitalization is shorter than in Japan. However, our finding that slower IVIG infusion was associated with faster fever resolution may be noteworthy even in settings where rapid infusion is the standard practice.

Fourth, our study period included the first year of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Although patients diagnosed with multisystem inflammatory syndrome in children (MIS-C) were excluded, the possibility remains that a small number of MIS-C cases were misclassified as KD. However, MIS-C is a rare complication in East Asia[13], and Japanese national surveillance data suggest that SARS-CoV-2–related KD is extremely rare[14].

Lastly, variations may have existed among institutions in terms of the timing of temperature assessments and the determination of implementing additional treatments owing to its multicenter and retrospective design. An equal distribution of patients from each institution was planned within the 10% and 5% immunoglobulin groups to minimize the potential influence of these institutional differences on the outcomes. Additionally, patients in the 10% immunoglobulin group were treated more recently than those in the 5% immunoglobulin group. Although we cannot completely dismiss the potential impact of this disparity in treatment period on the findings, we have verified with each institution that no modifications were made to their KD treatment or care protocols throughout the study period.

In conclusion, the group that used 10% immunoglobulin products showed a shorter duration of IVIG infusion and a higher prevalence of IVIG nonresponders regardless of the preexisting risk score; however, it did not influence CAL incidence. Considering that prompt resolution of inflammation contributes to a decrease in CALs, the outcomes of this study could influence CAL incidence when assessed across a larger patient population. Therefore, validation through a comprehensive prospective study is warranted.

Methods

Study design

From April 1, 2015, to March 31, 2021, patients aged 0–15 years who were diagnosed with KD or incomplete KD and who received 2 g/kg of IVIG in a single continuous infusion for primary treatment within 9 days of illness onset were enrolled at 9 general hospitals located in the Aichi prefecture of Japan. All hospitals switched over from 5 to 10% immunoglobulin products and continued using the 10% product thereafter. Each hospital enrolled a maximum of 80 patients (40 in each of the 5% and 10% immunoglobulin groups), with 40 consecutive patients in each group before and after the first use of 10% immunoglobulin products for KD treatment. Hospitals with fewer than 40 patients in either group enrolled the same number of patients in both groups (Supplementary Fig. S1B). Patients with CALs at the start of primary treatment, steroid use within 30 days, or immunoglobulin use within 180 days before primary treatment initiation were excluded.

The medical records of patients were reviewed to retrieve data regarding the following: (1) demographic characteristics; (2) clinical presentation and findings at diagnosis; (3) details of treatment; (4) outcome information; and (5) information on AEs. Data of patients who underwent multiple laboratory examinations before diagnosis were collected for the lowest values of hemoglobin, hematocrit, platelet count, total protein, albumin, and sodium, and the highest values of white blood cell count, neutrophil percentage, C-reactive protein, aspartate transaminase, and alanine transaminase.

The time from the start of IVIG administration to fever resolution was the primary outcome of the study. The interval between primary and secondary treatments, frequency of nonresponse to primary treatment and relapse, frequency of CALs within and at 28 days after primary treatment, and AEs of IVIG were the secondary outcomes.

This study was approved by the ethics committee of Nagoya University Graduate School of Medicine (2021 – 0139). Due to the retrospective nature of the study, informed consent was obtained through an opt-out option on the website, and participants who refused consent were excluded. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Definition

The diagnosis of KD and incomplete KD were made on the basis of the current Japanese diagnostic guidelines for KD[15]. The first day of illness was defined as the day of fever onset. Fever was defined as an axillary temperature of 37.5 °C or higher. Fever resolution was defined as a temperature of less than 37.5 °C for at least 24 h, and the time of fever resolution was defined as the first time the axillary temperature fell below 37.5 °C when it could be judged that the fever had resolved. According to the current Japanese guidelines, nonresponse to primary treatment was defined as persistent fever for 48 h after start of the IVIG administration[4]. Relapse of KD was defined as the recurrence of fever with major KD symptoms after the fever once resolved, and other causes were ruled out. The interval between primary and secondary treatments was defined as the time between the start of primary treatment and the start of secondary treatment. CALs were defined according to the current Japanese guideline on the diagnosis of cardiovascular sequelae in KD, using Z-scores calculated from coronary artery inner diameters, with CAL defined as a Z-score ≥ 2.5[16]. Severe AEs were defined on the basis of criteria used in previous studies[8].

Treatment

Patients were treated at each hospital in accordance with the Japanese guidelines for medical treatment of acute KD[4,17]. Primary treatment comprised 2 g/kg IVIG in a single continuous infusion and 30 mg/kg aspirin daily. The aspirin dose was reduced to 3–5 mg/kg per day following fever resolution. As described in the Japanese guideline for medical treatment of acute KD, patients with a Kobayashi score of ≥ 5 points, indicating a high risk of nonresponse to IVIG, were allowed to receive concurrent steroids with IVIG at the discretion of the institution or treating physician[4,8]. Although the time intervals for temperature measurement during KD treatment were not standardized among the hospitals, there was no change in the policy of each hospital during this study period.

Statistical analysis

Categorical variables were compared using Fisher's exact test and continuous variables using the Mann–Whitney U test, and analyses adjusted for contextual factors were performed by logistic regression analysis. To exclude the effect of secondary treatment on fever resolution, the cumulative incidence of fever resolution was calculated using the competing risk methods, with the start of secondary treatment as the competing event. Gray's test was used for group comparisons of cumulative incidences. Additionally, the cumulative incidence of fever resolution to each time point was evaluated using the Gray's test by censoring patients who had not achieved fever resolution at that specific time point. All tests were two-tailed, and a type I error of < 0.05 indicated statistical significance. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan[18].

Data availability

The datasets generated during the current study are available from the corresponding author upon reasonable request.

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Author contributions

DS conceptualized and designed the study, acquired data, analyzed and interpreted the data, produced figures, and drafted the initial manuscript. NN and TK conceptualized and designed the study, interpreted the data, and reviewed and revised the manuscript. TH and KS conceptualized and designed the study and collected data. FK and KG conceptualized and designed the study, and critically reviewed the manuscript. HK, JK, YS, and YT supervised the study and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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