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CLINICAL FEATURE
ORIGINAL RESEARCH

Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status

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ABSTRACT

Objective: Kawasaki disease (KD) is a systemic vasculitis with serious complications, especially the development of coronary artery lesions (CALs). The aim of this study was to identify the risk for the development of CALs with IVIG treatment of KD >10 days after illness onset in patients with different KD status, and explore potential moderators of the association between delayed treatment and CALs.

Methods: We performed a retrospective review of the medical records of KD patients. All patients were divided into two groups (conventional therapy group and delayed therapy group, IVIG treatment ≤10 days vs >10 days). We compared the demographic and clinical characteristics, laboratory data, and analyzed risk factors for CALs in patients who received IVIG treatment >10 days, and determined whether different status of KD modified the effects of delayed IVIG treatment on CALs.

Results: In the delayed IVIG treatment group, children were more likely to develop CALs and the proportion of incomplete KD was higher, compared with the conventional therapy group. The number of children younger than 12 months or older than 61 months was higher and children had higher BMI and were more likely to receive steroids before diagnosis in the delayed IVIG treatment group compared with the conventional therapy group. Delayed IVIG treatment was an independent risk factor for the development of CALs (adjusted OR = 2.90, 95%CI = 1.42, 5.91). Delayed therapy children with higher levels of C-reactive protein (>79 mg/L) and erythrocyte sedimentation rate (>34 mm/h) had the highest risk for developing CALs (OR = 5.68, 95%CI: 1.17, 27.59; OR = 4.11, 95%CI: 1.62, 10.46, respectively).

Conclusion: Delayed IVIG treatment was an independent risk factor for the development of CALs. Children in the delayed IVIG treatment group with higher levels of CRP and ESR (CRP >79 mg/L, ESR >34 mm/h) had the greatest likelihood of developing CALs.

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Kawasaki disease; coronary artery lesions; delayed immunoglobulin therapy; C-reactive protein; erythrocyte sedimentation rate

Introduction

Kawasaki disease (KD) is an acute febrile illness with systemic vasculitides that primarily affects infants and young children, and is the leading cause of acquired heart diseases [1,2]. The major serious complication of KD is coronary artery lesions (CALs) [3], which can cause coronary aneurysms in the acute phase and induce long-term sequelae-like coronary stenosis or obstruction [2,4,5]. Despite receiving intravenous immunoglobulin (IVIG) therapy, CALs occur in 5–20% of patients with KD during the acute stage [6–8]. According to the guidelines of the American Heart Association and American Academy of Pediatrics and previous reports, IVIG and aspirin have been established as the most effective therapies for acute KD as they control inflammation and reduce the risk of CALs [9–13].

Because coronary artery changes usually begin on days 7–10 after illness onset, treatment within 10 days, especially within 7 days, of illness onset is optimal [14,15]. And patients with KD who received IVIG <5 days after illness onset may be more likely to resistant to IVIG [16]. However, approximately 10–25% of KD patients diagnosed with KD are administered IVIG >10 days after illness onset [17–23], and Muta et al. [12] reported that patients who received delayed IVIG treatment had higher risk to develop CALs during the convalescent phase (27% vs. 1%), but among patients who had not developed CALs before initial treatment, the proportions with CALs during the acute phase were similar (8% vs. 8%). More importantly, few studies have investigated whether the association between delayed IVIG treatment and CALs is modified by the status of KD, such as the levels of C-reactive protein (CRP), white blood cells (WBC), and other factors.

In the current study, we aimed to identify the risk for the development of CALs in association with IVIG treatment of KD >10 days after illness onset, and explore potential moderators of the association between delayed treatment and CALs.

Methods

This study was approved by the Ethical Board of Wenzhou Medical University, Zhejiang, China. Informed consent was signed by the parents of all patients.

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Subjects

We performed a retrospective review of the medical records of 930 consecutive KD inpatients initially treated with IVIG and aspirin, from January 2009 to December 2014, at Wenzhou Medical University Second Affiliated Hospital & Yuying Children's Hospital, Wenzhou, China. The number of patients followed for 6 months and 1 year were 578 and 332, respectively. All patients who met the fever criterion and at least four of the five principal criteria were classified as complete KD (cKD); patients with less than four principal clinical criteria excluding illnesses with similar clinical features to KD were classified as incomplete KD (iKD) [8]. Time of IVIG treatment was defined as the duration between the fever onset and IVIG treatment. All patients were classified into two groups: conventional therapy group (received IVIG treatment ≤10 days) and delayed therapy group (received IVIG treatment >10 days). Of these patients, 871 received initial IVIG therapy ≤10 days and 59 received initial IVIG therapy 10 days after the onset of illness.

Data collection

We collected the following information including age (months), gender, BMI (kg/m^2), type of KD, length of hospitalization (days), and whether patients received steroids before admission to hospital. Additionally, a change in medical department was also collected: if the patient directly went to a pediatric cardiovascular department, it was reported as no change of medical department and coded as 0; otherwise, if they went to an emergency or other department first, and were then transferred to a cardiovascular department, it was coded as 1. Duration of fever at admission to hospital was also extracted, indicating whether patients sought treatment in time. We also collected laboratory data including the erythrocyte sedimentation rate (ESR), CRP, WBC count, percentage of neutrophils (NEUT%), number of neutrophils (NEUT), red blood cell (RBC) count, and levels of albumin (ALB), aspartate transaminase (AST), and alanine transaminase (ALT) at baseline. Patients were divided into high and low groups in the conventional and delayed therapy groups according to the median values of their laboratory data. We also determined whether receiving steroid therapy before diagnosis and changing medical department modified the effects of delayed IVIG therapy on CALs.

The diagnosis of CALs is based on the following three criteria: (1) coronary artery diameter >2.5 mm in children <3 years old, >3mm in children aged 3–9 years, and >3.5 mm in children older than 9 years; as well as diameter of one segment of coronary artery more than 1.5 times that of adjacent segment; (2) coronary artery aneurysm: ratio of the diameter of the coronary artery to the adjacent segment > 1.5, and diameter of the coronary artery >4 mm. Small, medium, and giant coronary artery aneurysm are defined based on the coronary artery diameter: <5, 5–8, and >8, respectively; (3) coronary artery stenosis and embolism: coronary artery diameter reduction, irregular and asymmetric tube wall or irregularity and interruption of the lumen of the continuous non-echo area.

Statistical methods

Continuous variables were compared using the *t*-test or Mann–Whitney *U* test as appropriate; categorical variables were compared using the chi-square test or Fisher's exact test. Independent effects of treatment time on CALs were examined using multiple logistic regression models. Confounding effect was assumed if the effect size of treatment time on CALs changed by ≥10% when adding potential confounders. Statistical analyses were performed with IBM SPSS Statistics 23, Empower(R) (X & Y solutions Inc., Boston, MA, USA) and R (http://www.R-project.org). All tests were considered significant when $P < 0.05$.

Results

Characteristics of the study patients

A total of 930 patients were included in this study; of these, 59 were treated with IVIG >10 days after fever onset and the proportion of delayed IVIG therapy was 6.3%. Table 1 shows a comparison of characteristics between the conventional therapy group and delayed therapy group. The proportion of iKD cases in the delayed therapy group was significantly higher than in the conventional therapy group. The proportions of principal symptoms other than changes of the extremities were lower in the delayed therapy group than in the conventional therapy group. Overall, 28.8% of patients in the delayed therapy group received steroids therapy before being diagnosed as KD, and this proportion was much higher than in the conventional therapy group. The incidence of CALs in the delayed therapy group was 42.4% at 1 month after the onset of KD, which was higher than in the conventional therapy group. Length of hospitalization was longer in the delayed therapy group compared with the conventional therapy group. We divided patients into four groups by BMI (≤15.6, 15.7–17.1, 17.2–18.9, >19 kg/m^2). The proportion of BMI >19.0 kg/m^2 was higher in the delayed therapy group compared with the conventional therapy group. There was no difference in average age between the two groups, but there was a larger proportion of patients younger than 12 months or older than 61 months in the delayed therapy group compared with the conventional therapy group. There was no statistically significant difference in gender ratio between the two groups.

Risk factors for CALs

Table 2 shows the univariate analysis of risk factors for CALs at different times of disease. We found that male children were more likely to develop CALs at 1 (odds ratio, OR = 1.74, 95% confidence interval, 95%CI = 1.21, 2.50) and 6 months (OR = 3.50, 95%CI = 1.54, 7.95) after illness onset, compared with female children; however, there was no difference at 1 year after illness onset. To analyze whether age was associated with CALs, we divided patients into three groups based on age (≤12, 13–60, >61 months); however, there was no difference between the three groups. We also found that increased BMI was associated with CALs at 1 (OR = 1.08, 95%CI = 1.02, 1.15) and

Table 1. Characteristics of children with KD based on the time of IVIG treatment.

Characteristics	≤10 days therapy (n = 871)	>10 days therapy (n = 59)	P value
Age (months)	19.00 (10.00–32.50)	17.00 (7.50–37.00)	0.598
Age-group (months)			0.028
≤12	274 (31.50)	24 (40.70)	
13–60	537 (61.70)	27 (45.80)	
≥61	60 (6.90)	8 (13.60)	
Gender			0.285
Female	309 (35.50)	25 (42.40)	
Male	562 (64.50)	34 (57.60)	
BMI (kg/m^2)	17.43 ± 2.73	17.58 ± 3.48	0.677
BMI group (kg/m^2), n (%)			0.017
≤15.6	209 (24.00)	22 (37.30)	
15.7–17.1	225 (25.80)	9 (15.30)	
17.2–18.9	224 (25.70)	9 (15.30)	
≥19.0	213 (24.50)	19 (32.20)	
KD type			<0.001
Complete	551 (63.30)	21 (35.60)	
Incomplete	320 (36.70)	38 (64.40)	
The number of signs	5.00 (5.00–6.00)	4.00 (4.00–6.00)	<0.001
Polymorphous rash (yes, %)	664 (76.30)	36 (61.00)	0.008
Bilateral conjunctival injection (yes, %)	779 (89.50)	36 (61.00)	<0.001
Changes of the oral mucosa, lips, and tongue (yes, %)	840 (96.60)	46 (78.00)	<0.001
Changes of extremities (yes, %)	547 (62.90)	41 (69.50)	0.307
Cervical lymphadenopathy (yes, %)	422 (48.50)	18 (30.50)	0.007
Change of medical departments (yes, %)	83 (9.50)	5 (8.50)	0.789
Duration of hospitalization (days)	12.00 (10.00–13.00)	13.00 (10.00–16.00)	<0.001
Steroids before diagnosis (yes, %)	152 (17.50)	17 (28.80)	0.029
CALs at 1 m (yes, %)	154 (17.70)	25 (42.40)	<0.001

Quantitative data were expressed as mean ± SD if normally distributed, otherwise as median (interquartile range), and qualitative data were expressed as frequency (%).

KD: Kawasaki disease; CAL: coronary artery lesion; BMI: body mass index; IVIG: intravenous immunoglobulin; SD: stantard deviation.

6 months after illness onset (OR = 1.14, 95%CI = 1.03, 1.25), but there was no difference at 1 year after illness onset. Then, we divided patients into four groups according to BMI (BMI ≤15.6; 15.7–17.1; 17.2–18.9; >19 kg/m^2), and found that patients with BMI >19 kg/m^2 were more likely to develop CALs at 1 (OR = 1.84, 95%CI = 1.17, 2.88), 6 months (OR = 2.14, 95% CI = 0.99, 4.58), and 1 year (OR = 5.18, 95%CI = 1.09, 24.71) after illness onset. Furthermore, children presenting as iKD were more likely to develop CALs at 1 (OR = 1.50, 95%CI = 1.08, 2.08) and 6 months (OR = 2.08, 95%CI = 1.16, 3.76) after illness onset. Of 930 patients, the mean number of days with fever (duration of fever at admission to hospital) was 5.03 ± 2.35, and an increase in duration of fever was associated with CALs at 1 (OR = 1.18, 95%CI = 1.10, 1.25) and 6 months (OR = 1.18, 95% CI = 1.07, 1.30) after illness onset. All patients received IVIG treatment on mean day 6.99 ± 2.27 after illness onset, and the risk for CALs at 1 month after illness onset increased 1.17% (95% CI = 1.10, 1.25) per 1 day delay of IVIG treatment and the risk for CALs at 6 months increased 1.17% (95%CI = 1.06, 1.28) per 1 day delay in IVIG treatment. If patients received IVIG treatment >10 days after illness onset, the CAL risk at 1 month after illness onset was 3.42 times greater than for those who received IVIG therapy ≤10 days. Eighty-eight patients were not admitted to a cardiology department directly, and they had a higher risk for developing CALs at 1 and 6 months, but not 1 year, after illness onset. Children that received steroid therapy before diagnosis had no association with CALs.

Effects of time of IVIG treatment and delayed IVIG treatment on CALs

Logistic analysis was performed for the correlation between treatment time and CALs, and delayed IVIG treatment and CALs. The results showed that treatment time was correlated

Table 2. Univariate analysis of CALs at different times after IVIG therapy.

Characteristics	CALs on 1 month (n = 930), OR (95%CI) P	CALs on 6 months (n = 578), OR (95%CI) P	CALs on 1 year (n = 332), OR (95%CI) P
Gender			
Female	1	1	1
Male	1.74 (1.21, 2.50) 0.003	3.50 (1.54, 7.95) 0.003	3.74 (0.83, 16.74) 0.085
Age (months)	0.99(0.98, 1.00) 0.199	0.99(0.98, 1.01) 0.264	1.00(0.98, 1.02) 0.917
Age-group (months)			
≤12	1	1	1
13–60	1.00 (0.70, 1.43) 0.989	0.89 (0.48, 1.67) 0.724	0.73 (0.25, 2.18) 0.579
≥61	0.80 (0.39, 1.62) 0.532	0.69 (0.19, 2.45) 0.561	1.17 (0.22, 6.12) 0.850
BMI (kg/m^2)	1.08 (1.02, 1.15) 0.005	1.14 (1.03, 1.25) 0.011	1.17 (0.99, 1.38) 0.059
BMI group (kg/m^2)			
≤15.6	1	1	1
15.7–17.1	0.81 (0.49, 1.34) 0.408	0.47 (0.16, 1.40) 0.178	1.30 (0.18, 9.46) 0.796
17.2–18.9	1.15 (0.71, 1.84) 0.574	1.13 (0.47, 2.69) 0.785	1.80 (0.29, 11.03) 0.527
≥19.0	1.84 (1.17, 2.88) 0.008	2.14 (0.99, 4.58) 0.051	5.18 (1.09, 24.71) 0.039
Duration of fever(days)	1.18 (1.10, 1.25) <0.001	1.18 (1.07, 1.30) 0.001	1.08 (0.92, 1.28) 0.345
KD type			
Complete KD	1	1	1
Incomplete KD	1.50 (1.08, 2.08) 0.016	2.08 (1.16, 3.76) 0.014	2.22 (0.80, 6.11) 0.124
Treatment time (days)	1.17 (1.10, 1.25) <0.001	1.17 (1.06, 1.28) 0.002	1.11 (0.94, 1.31) 0.226
Delayed treatment (yes/no)	3.42 (1.99, 5.90) <0.001	2.41 (0.95, 6.11) 0.065	1.82 (0.39, 8.50) 0.446
Change of medical departments[a] (yes/no)	1.77 (1.08, 2.91) 0.023	2.25 (1.03, 4.93) 0.041	1.23 (0.27, 5.63) 0.794
Steroids before diagnosis (yes/no)	1.22 (0.81, 1.84) 0.335	1.19 (0.57, 2.46) 0.646	1.12 (0.31, 4.06) 0.864

[a]Change of medical departments: if the patient directly went to the pediatric cardiovascular department, it was regarded as no change of medical department, and coded 0; otherwise if they went to the emergency or other department first, and then transferred to the cardiovascular department, it was coded 1.

KD: Kawasaki disease; IVIG: intravenous immunoglobulin; CAL: coronary artery lesion; BMI: body mass index; OR: odds ratio; 95%CI: 95% confidence interval.

with risk of CALs at 1 and 6 months after illness onset (OR = 1.18, 95%CI = 1.10, 1.26, $P < 0.001$; OR = 1.17, 95% CI = 1.06, 1.29, $P = 0.001$), after adjustment for age and gender. We further adjusted for possible confounding factors that might be associated with CALs, such as age, gender, KD-type (cKD or iKD), BMI, and whether the patient changed therapy department. Treatment time remained a significant risk factor for CALs at 1 and 6 months after illness onset. We also analyzed the correlation between delayed IVIG treatment and CALs, and found that children with KD who received IVIG therapy >10 days after illness onset were 2.9 times likely to develop CALs at 1 month, but not 6 months and 1 year after illness onset, compared with children who received IVIG therapy ≤10 days (Table 3).

Interaction analysis of delayed IVIG treatment and other status of KD with CALs

We compared children who received IVIG treatment ≤10 days with CRP below 79 mg/L and delayed IVIG treatment children with a high level of CRP (>79 mg/L). We found that delayed IVIG treatment with high CRP levels had a higher risk for developing CALs (OR = 5.68, 95%CI = 1.17, 27.59; $P < 0.05$). Delayed IVIG therapy in children with high levels of ESR (>34 mm/h) also had higher risk of developing CALs (OR = 4.11, 95%CI = 1.62, 10.46; $P < 0.05$) compared with children who received IVIG ≤10 days with ESR ≤34 mm/h. We found that delayed therapy in children with low levels of ALB (<32.4 g/L) had an increased but not significant risk of developing CALs (OR = 2.72, 95%CI = 1.07, 6.93; $P > 0.05$) compared with children with ALB >32.4 g/L in the conventional therapy group. High numbers of neutrophils (>10.7 × 10^9/L) with delayed therapy was also risk factor for CALs compared with children with a lower number of neutrophils (<10.7 × 10^9/L) who received IVIG therapy ≤10 days (OR = 5.28, 95%CI = 1.41, 19.84), but the P value was >0.05. Low levels of RBC (<4.11 × 10^{12}/L) in the delayed therapy group was a risk factor for CALs compared with children with higher levels of RBC (>4.11 × 10^{12}/L) and who received IVIG therapy ≤10 days (OR = 3.71, 95%CI = 1.46, 9.42), but the P value was >0.05. High levels of RBC in the conventional therapy group were protective against CAL (OR = 0.31, 95% CI = 0.10, 0.97). Compared with low levels of AST in the conventional therapy group, the other three groups had a higher risk of developing CALs, especially in the delayed therapy group with high levels of AST (OR = 8.43, 95% CI = 2.07, 34.41), but the P value was >0.05. Compared with no change of department in the conventional therapy group, the other three groups had a higher risk of developing CALs, especially the delayed therapy group with a change in department, which had the highest risk (OR = 16.27, 95% CI = 1.05, 252.63), but the P value was >0.05. No interaction effects were found for WBC, NEUT%, ALT and whether received steroids before IVIG treatment (Table 4).

Discussion

KD is a systemic vasculitis, with complications including the development of coronary artery aneurysms, which in severe cases may be fatal. In Japan, the proportion of children with complications was reduced from 18% in 1997 to 12% in 2006 [24]. IVIG is effective at interrupting vascular inflammation in the acute stage of illness, and treatment within 10 days of fever was identified as an appropriate cutoff point for IVIG administration [9]. However, some patients cannot receive IVIG treatment within 10 days, and the latest literature reported the proportion of delayed IVIG therapy was 18.9% [23]. In addition, the incidence of CALs among these patients was reported to be higher than among patients treated earlier, indicating this is a risk factor for CALs [17,25–27]. In this study, we identified risk factors for the development of CALs at different time points related to the IVIG treatment of KD >10 days after illness onset. We collected 6-year retrospective medical records for 6.3% of patients receiving IVIG treatment >10 days after illness onset, which was lower than previously reported [17–23]. In our study, we found the incidence of CALs in the delayed IVIG therapy group was higher than in the conventional therapy group. Previous reports indicated that younger children (6 months of age) and iKD cases were more likely to receive IVIG treatment >10 days after illness onset [18,22], consistent with our study. We found that children younger than 12 months or older than 61 months presenting as iKD had a higher likelihood of receiving IVIG treatment >10 days. We also found that patients with higher BMI were more likely to receive IVIG treatment >10 days. Higher numbers of patients in the delayed therapy group received steroids before diagnosis compared with the conventional therapy group. Steroids may reduce vasculitis symptoms leading to delayed diagnosis and therapy.

We analyzed factors that may affect CALs at different time points. We found that male patients, patients with a higher BMI, patients presenting as iKD and delayed IVIG therapy were associated with CALs at 1 and 6 months after illness onset. Chen et al. reported that BMI was associated with further

Table 3. Independent effect of delayed IVIG treatment on CALs.

Model	CALs on 1 month (n = 930), OR (95%CI) P	CALs on 6 months (n = 578), OR (95%CI) P	CALs on 1 year (n = 332), OR (95%CI) P
Model I			
Treatment time (days)	1.18 (1.10, 1.26) <0.001	1.17 (1.06, 1.29) 0.001	1.10 (0.93, 1.30) 0.276
Treatment time (>10 vs. ≤10 days)	3.71 (2.13, 6.45) <0.001	2.81 (1.08, 7.35) 0.035	1.87 (0.39, 8.92) 0.431
Model II			
Treatment time (days)	1.13 (1.04, 1.22) 0.006	1.15 (1.01, 1.30) 0.031	1.15 (0.94, 1.39) 0.173
Treatment time (>10 vs. ≤10 days)	2.90 (1.42, 5.91) 0.003	2.43 (0.78, 7.59) 0.128	2.61 (0.44, 15.47) 0.290

Model I adjustment factors: age, gender.
Model II adjustment factors: age, gender, type of KD, BMI, change in department and type of IVIG treatment.
KD: Kawasaki disease; IVIG: intravenous immunoglobulin; CAL: coronary artery lesion; BMI: body mass index; OR: odds ratio; 95%CI: 95% confidence interval.

Table 4. The interaction analysis for delayed therapy and the potential factors on CALs within 1 month.

Factors	Delayed IVIG treatment	*n*	CAL%	aOR[a] (95%CI)	*P*	*P* (interaction)
ESR (mm/h)						0.017
≤34	No	344	19.2	1.0 (ref.)		
≤34	Yes	20	22.7	1.31 (0.45, 3.78)	0.618	
>34	No	366	17.0	0.91 (0.62, 1.35)	0.650	
>34	Yes	17	50.0	4.11 (1.62, 10.46)	0.003	
CRP (g/L)						0.008
≤79	No	421	20.1	1.0 (ref.)		
≤79	Yes	41	31.0	1.36 (0.57, 3.26)	0.491	
>79	No	446	15.5	0.52 (0.18, 1.51)	0.230	
>79	Yes	18	70.6	5.68 (1.17, 27.59)	0.031	
WBC ($\times10^9$/L)						0.115
≤16.5	No	435	17.7	1.0 (ref.)		
≤16.5	Yes	28	35.7	1.50 (0.57, 3.96)	0.412	
>16.5	No	432	17.8	0.71 (0.25, 2.02)	0.521	
>16.5	Yes	31	48.4	3.18 (0.85, 11.88)	0.085	
ALB (g/L)						0.678
≤32.4	No	413	18.9	1.0 (ref.)		
≤32.4	Yes	30	51.6	2.72 (1.07, 6.93)	0.035	
>32.4	No	422	16.0	0.54 (0.17, 1.67)	0.285	
>32.4	Yes	27	29.6	1.09 (0.25, 4.72)	0.910	
NEUT%						0.209
≤0.67	No	418	19.3	1.0 (ref.)		
≤0.67	Yes	34	38.2	1.78 (0.73, 4.34)	0.207	
>0.67	No	446	15.9	0.78 (0.27, 2.23)	0.643	
>0.67	Yes	24	50.0	3.43 (0.80, 14.69)	0.097	
NEUT ($\times10^9$/L)						0.353
≤10.7	No	433	17.3	1.0 (ref.)		
≤10.7	Yes	27	37.0	2.00 (0.74, 5.41)	0.174	
>10.7	No	430	17.9	1.38 (0.49, 3.92)	0.543	
>10.7	Yes	30	50.0	5.28 (1.41, 19.84)	0.014	
RBC ($\times10^{12}$/L)						0.464
≤4.11	No	408	20.0	1.0 (ref.)		
≤4.11	Yes	31	54.8	3.71 (1.46, 9.42)	0.006	
>4.11	No	431	14.8	0.31 (0.10, 0.97)	0.045	
>4.11	Yes	27	29.6	0.68 (0.17, 2.73)	0.586	
AST (IU/L)						0.663
≤30	No	422	17.1	1.0 (ref.)		
≤30	Yes	30	45.2	3.02 (1.08, 8.45)	0.036	
>30	No	436	18.1	3.80 (1.19, 12.15)	0.024	
>30	Yes	29	39.3	8.43 (2.07, 34.41)	0.003	
ALT (U/L)						0.760
≤34	No	416	17.0	1.0 (ref.)		
≤34	Yes	37	39.5	2.31 (0.92, 5.78)	0.074	
>34	No	445	18.0	1.31 (0.45, 3.78)	0.619	
>34	Yes	22	47.6	3.76 (0.92, 15.36)	0.065	
Received steroids therapy						0.388
No	No	719	17.7	1.0 (ref.)		
No	Yes	42	35.7	2.11 (0.95, 4.71)	0.068	
Yes	No	152	17.8	1.47 (0.38, 5.63)	0.576	
Yes	Yes	17	58.8	6.20 (0.90, 42.63)	0.064	
Change of medical department						0.923
No	No	788	16.8	1.0 (ref.)		
No	Yes	54	40.7	3.42 (1.90, 6.16)	<0.001	
Yes	No	83	26.5	1.79 (1.05, 3.05)	0.032	
Yes	Yes	5	60.0	7.29 (1.85, 45.17)	0.033	

IVIG treatment time: if a patient received IVIG treatment >10 days it was coded as yes; otherwise if they received IVIG treatment ≤10 days it was coded as no.
Change department: if the patient directly went to a pediatric cardiovascular department, it was regarded as no change in medical department, and coded as no; otherwise, if they went to an emergency or other department first, and were then transferred to a cardiovascular department, it was coded as yes.
[a]Adjustment for the effects of age and gender.
CAL: coronary artery lesion; aOR: adjusted odds ratio; 95%CI: 95% confidence interval; ALT: alanine transaminase; AST: aspartate transaminase; WBC: white blood cell; RBC: red blood cell; ALB: albumin; NEUT: number of neutrophils; NEUT%: percentage of neutrophils; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

cardiovascular events of KD [28]. We found that a BMI >19 kg/m^2 had a higher risk for CALs even at 1 year after illness onset. Our logistic analysis indicated that treatment time was a significant risk factor for CALs at 1 and 6 months after illness onset. Patients receiving IVIG therapy >10 days after illness onset were 2.9 times more likely to develop CALs at 1 month after illness onset compared with children who received IVIG therapy ≤10 days, and they still had tendency to develop CALs at 6 months and 1 year after illness onset, although this was significantly different between groups.

This study and many previous reports indicated that delayed IVIG treatment is a risk factor for CALs, but whether the effects are modified by the status of KD is unclear. Therefore, we analyzed whether IVIG treatment time with different levels of ESR, CRP, WBC, NEUT%, number of neutrophils, RBC, ALB, AST, and ALT had different effects on the risk of developing CALs. We

also analyzed whether receiving steroids therapy before diagnosis and change in medical department modified the effects of delayed therapy on the risk of developing CALs. The strongest effects were observed for high CRP and ESR: there was a 5.68% and 4.11% increase in the risk of CALs in the delayed IVIG treatment group with high levels of CRP and ESR.

This study had several limitations. First, the study results might be limited by the retrospective design and that all patients were from a single Pediatric Cardiac Clinic, which might cause selection bias. Second, only initial laboratory measurements were analyzed in the present study. Third, only 30% of patients were followed for 1 year, and the missed follow-up rate was high.

Conclusion

Younger or older children and patients presenting as iKD had a high possibility for receiving IVIG treatment at 10 days after illness onset. Administration of IVIG after 10 days of illness onset increased the risk of CALs at 1 month. IVIG treatment time was an independent risk factor for CALs. Patients with high levels of CRP and ESR and receiving IVIG treatment at 10 days after illness onset were considered to have the highest risk of developing CALs.

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Declaration of interest

The authors have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. Postgraduate Medicine peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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