

## Original Article

### Prognosis and Risk Factors of Coronary Artery Lesions before Treatment Among Patients with Kawasaki Disease

Huixian Qiu<sup>1#</sup>, Jia Chang<sup>1#</sup>, Zhenquan Wang<sup>1</sup>, Yuee He<sup>1</sup>, Xing Rong<sup>1</sup>, Rongzhou Wu<sup>1</sup>, Maoping Chu<sup>1\*</sup>, Hongying Shi<sup>2\*</sup>

<sup>1</sup>Children's heart center, the second affiliated Hospital & Yuying Children's Hospital, Institute of Cardiovascular Development and Translational Medicine, Wenzhou Medical University, Wenzhou, Zhejiang, China.

<sup>2</sup>Department of Preventive Medicine, School of Public Health and Management, Wenzhou Medical University, Zhejiang Province, China

<sup>#</sup>These authors contributed equally to this work

**Address for Correspondence:** Maoping Chu, Children's Heart Center, The Second Affiliated Hospital and Yuying Children's Hospital, Institute of Cardiovascular Development and Translational Medicine, Wenzhou Medical University, Wenzhou 325027, Zhejiang, China

Email: [chmping@hotmail.com](mailto:chmping@hotmail.com)

Hongying Shi, Department of Preventive Medicine, School of Public Health and Management, Wenzhou Medical University, Wenzhou 325027, Zhejiang Province, China.

Email: [shying918@163.com](mailto:shying918@163.com)

**Received:** 02 February 2020

**Accepted:** 28 July 2020

**DOI:** [10.4274/balkanmedj.galenos.2020.2020.1.56](https://doi.org/10.4274/balkanmedj.galenos.2020.2020.1.56)

**Cite this article as:** Qiu H, Chang J, Wang Z, He Y, Rong X, Wu R, Chu M, Shi H. Prognosis and Risk Factors of Coronary Artery Lesions before Treatment Among Patients with Kawasaki Disease. *Balkan Med J*

**Background:** Many children with Kawasaki disease (KD) had already developed coronary artery lesions (CAL) before intravenous immunoglobulin (IVIG) treatment. However, little data are available on the prognosis of KD children who developed CAL before IVIG treatment.

**Aims:** To explore the outcomes of CAL before IVIG treatment in children with Kawasaki disease (KD) and analyze the factors that influence the duration of CALs.

**Study design:** Retrospective cross-sectional study.

**Methods:** All patients with KD who had developed CAL before IVIG treatment in our hospital from January 2009 to December 2014 were reviewed. A Cox proportional risk model was used to determine the factors influencing the prognosis of CAL.

**Results:** Among 182 patients included, 28.6% were male and 83.50% were <36 months old, 181 exhibited resolution of CAL 2 years after disease onset. The median duration of CALs was 31 days, and the proportion of CAL was 52% at 1 month, 35% at 2 months, 33% at 3 months, 25% at 6 months, 14% at 1 year, and 0.5% at 2 years. The univariate analysis showed that an overweight status, higher platelet count, lower albumin level, and receiving treatment later than 10 days after disease onset were the factors possibly affecting the duration of CAL

in children. The multivariate Cox regression analysis showed that female sex [adjusted HR, 1.661; 95% CI, 1.117–2.470] was an independent protective factor and that an overweight status (adjusted HR, 0.469; 95% CI, 0.298–0.737), higher platelet count (adjusted HR, 0.649; 95% CI, 0.443–0.950), and treatment later than 10 days after disease onset (adjusted HR, 0.392; 95% CI, 0.215–0.716) were independent risk factors for a longer duration of CAL.

**Conclusion:** The median duration of CAL before IVIG treatment in children with KD was 31 days. Male sex, an overweight status, a higher platelet count, and treatment later than 10 days after onset were independent risk factors for a longer duration of CAL.

**Keywords:** Kawasaki disease, coronary artery lesions, survival analysis, prognosis study

Kawasaki disease (KD) is often complicated with coronary artery damage (1,2). CAL affects the prognosis of children with KD and occurs in 25% to 30% of those with untreated KD (1,3,4). The cardiac prognosis is significantly improved by treatment of 2 g/kg of human intravenous immunoglobulin (IVIG) (5,6). A study in our department showed that the proportion of children with CAL in acute-stage was about 20% (7). Although left ventricular strain is impaired in patients with KD at a median follow-up of 57.5 months (8), but 99.8% of the children with maximum z scores of less than 2.5 at  $\leq 10$  days or 2 weeks would turn to normal on the 6 weeks of illness onset (9). We found that many children had already developed CAL before IVIG treatment. However, little data are available on the prognosis of patients with KD who developed CAL before IVIG treatment, including duration of CAL and what proportion of CAL will disappear, and the factors that influence the prognosis of CAL.

In this study, patients with KD who developed CAL before IVIG treatment were included, the duration of CAL, and the factors that influence the duration of CAL were analyzed.

## **Subjects and methods**

### **Subjects**

We collected medical records of all KD inpatients at our hospital, from 1 January 2009 to 31 December 2014. Patients who developed CAL before IVIG treatment were enrolled, and those who did not received IVIG treatment or did not have echocardiography findings both during hospitalization and after discharge were excluded.

All patients were treated with IVIG at a dose of 2 g/kg and aspirin (30–50 mg/kg per day), for IVIG-resistant patients, additional IVIG of 2 g/kg was administered. All patients were followed up for 2 years.

The diagnosis of complete KD is based on the presence of  $\geq 5$  days of fever and  $\geq 4$  of the following five symptoms (10): bilateral conjunctival injection without exudates; oral change; extremity changes; polymorphous rash; cervical lymphadenopathy. Patients with fever for  $\geq 5$  days and at least two of the principal features can be diagnosed with incomplete KD, if no other disease processes explain the illness.

The patients underwent echocardiographic examination at diagnosis (before IVIG treatment); 1 month  $\pm$  7 days after disease onset; and 2 months  $\pm$  7 days, 6 months  $\pm$  2 weeks, 1 year  $\pm$  1 month, and 2 years  $\pm$  1 month after disease onset. We collected the absolute dimensions of the proximal right coronary artery, left main coronary artery, and left anterior descending artery.

The diagnosis of CALs was based on the following three criteria in this study. (1) Coronary artery diameter of  $>2.5$  mm in children  $<3$  years old,  $>3.0$  mm in children 3 to 9 years old, and  $>3.5$  mm in children  $>9$  years old as well as the diameter of one segment of the coronary artery more than 1.5 times that of the adjacent segment.

(2) Coronary artery aneurysm: the ratio of the diameter of the coronary artery to the adjacent segment is  $>1.5$ , and the diameter of the coronary artery is  $>4$  mm. 3) Coronary artery stenosis and embolism.

### **Methods**

We collected the following informations: age at onset, gender, and body mass index (BMI). We collected clinical characteristics including the time of diagnosis, time of initial IVIG treatment, type of KD, and resistance to IVIG treatment. Additionally, any changes in the medical department were recorded. We also collected laboratory data including the platelet count, C-reactive protein (CRP) level, hemoglobin level, albumin level, and alanine transaminase level at baseline.

### **Statistical methods**

Quantitative variables are presented as mean  $\pm$  standard deviation if they were normally distributed, and presented as median (interquartile range) if they were not normally distributed. Qualitative variables are presented as frequency (percentage). CAL regression curves were drawn by the Kaplan–Meier method, and the differences in CAL regression among different groups were compared by the log rank test. The crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated by a Cox proportional hazards regression model to estimate the risk factors for prognosis of CAL before IVIG treatment in patients with KD. Data were analyzed with SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) and EmpowerStats (www.empowerstats.com; X&Y Solutions Inc.). All tests were two-sided and considered significant at the 0.05 level.

### **Results**

#### **Basic characteristics**

Among 182 patients included in the study, 28.6% were male and 83.50% were  $<36$  months old. The mean BMI was  $17.80 \pm 2.78$  kg/m<sup>2</sup>, and the proportion of overweight patients was 24.5%. Incomplete KD was present in 53.8% of patients. The CRP level was  $>150$  mg/L in 18.1% of patients, and the hemoglobin level was  $<100$  g/L in 19.2% of patients. The median time of diagnosis was 5 days [interquartile range (IQR), 4–7 days], and the median time of receiving IVIG treatment was 7 days (IQR, 6–9 days). Only nine patients (4.9%) were resistant to IVIG treatment (Table 1). No patients died during the follow-up period.

#### **Outcomes of patients with CALs before IVIG treatment**

The median duration of follow-up was 1 month (IQR, 1–3 months). The CAL of 181 patients ultimately disappeared, and the median time of recovery was 31.0 days (IQR, 17.8–44.2 days). In total, 52% of patients still had CAL at 1 month. The proportion of CAL at 2 months, 3 months, 6 months, and 1 year after illness onset was 35%, 33%, 25%, and 14%, respectively; by 2 years after onset, only 0.5% of patients still had CAL (Figure 1).

#### **Factors affecting the duration of CAL**

We then analyzed whether an overweight status had an effect on the duration of CAL. The results showed a higher proportion of CAL among overweight children than children of normal weight at the same time point ( $\chi^2 = 8.285$ ,  $P = 0.004$ ). We also found that patients who received IVIG treatment later than 10 days after onset required a longer time to recover to a normal clinical condition than those who received IVIG treatment within 10 days ( $\chi^2 = 5.702$ ,  $P = 0.017$ ). Patients with a lower albumin level ( $<28$  g/L) and higher platelet count ( $>450 \times 10^9/L$ ) had a longer duration of CALs than patients with an albumin level of  $\geq 28$  g/L and platelet count of  $\leq 450 \times 10^9/L$ . However, we found no evidence that age, sex, type of KD, change in medical departments, or hemoglobin level was associated with the duration of CAL (Figure 2).

#### **Factors affecting resolution of CAL before IVIG treatment**

The results from Cox regression model indicated that female sex was an independent protective factor (adjusted HR, 1.661; 95% CI, 1.117–2.470). An overweight status (adjusted HR, 0.469; 95% CI, 0.298–0.737), high platelet count (adjusted HR, 0.649; 95% CI, 0.443–0.950), and receiving IVIG treatment later than 10 days after onset (adjusted HR, 0.392; 95% CI, 0.215–0.716) were independent risk factors for resolution of CALs (Table 2).

## Discussion

In this study, we identified 930 patients with KD, 182 (19.6%) of whom developed CAL before IVIG treatment. The proportion of patients with CAL before IVIG treatment was lower than previously reported. de Ferranti et al(9) found that about 31.6% (318/1203) of patients had CAL at baseline (within 10 days of onset), most children were <3 years old, and the proportion of male children was 71.4%. In our study, we found the proportion of children <36 months old was 83.50%, the proportion of male children was 28.6%. Downie et al. (11) also reported that male children with delayed or no treatment were more likely to develop coronary artery aneurysms. In recent years, studies have shown that 5.0% to 38.3% of patients with KD are resistant to IVIG (12-14). In the present study, we found that 4.9% patients were resistant to IVIG treatment; this proportion is lower than in previous studies, during a follow-up of 2 years, the CAL of 181(181/182) patients ultimately disappeared, and the median time of recovery was 31.0 days.

Chbeir et al.(15) reported that about 31% of patients presented echocardiographic abnormalities, which were strongly associated with resistance to IVIG and development of CAL within the first 6 weeks of disease; however, they did not focus on the factors that influence the prognosis of CAL. We analyzed the prognosis of CAL before treatment and investigated the factors that possibly affect the duration of CAL. The BMI is a risk factor for cardiovascular events, and an excessive BMI increases cardiovascular mortality in adults and is associated with further cardiovascular events in patients with KD (16,17). Therefore, we analyzed the effect of weight on the prognosis of CAL, and the results indicated that overweight children had a higher proportion of CAL than children of normal weight at the same time point. Additionally, overweight children required a longer time to return to a normal clinical condition, which is consistent with our previous study (7,18). The platelet count has been used in a risk scoring system to predict IVIG resistance and coronary artery abnormalities (19-21). Bozlu et al showed that children with KD have lower mean platelet volume-to-lymphocyte ratio compared with control subjects [22]. The results obtain in this study, we found that the duration of CAL was longer in children with a higher platelet count, and a platelet count of  $>450 \times 10^9/L$  was an independent risk factor for prognosis of CAL. Previous studies have shown that a low albumin level is associated with CALs (23,24). We found that the proportion of CAL was higher in children with a low albumin level than in those with an albumin level of  $>28$  g/L, indicating that children with a low albumin level need more time to attain a normal clinical condition. Children with KD should receive IVIG treatment within 10 days of illness onset, and treatment within 7 days of onset is optimal (25,26). We found that the proportion of patients with incomplete KD was higher than that of patients with complete KD. Because of the lack of clinical manifestations in children with incomplete KD, they always undergo delayed diagnosis and treatment; thus, delayed IVIG treatment is associated with a higher risk of developing CAL during the convalescent phase (7,17,27). Our results also found that the duration of CAL was longer in children with delayed IVIG treatment.

Approximately 25% patients with KD develop serious coronary artery abnormalities, such as coronary artery aneurysm and ectasia, if left untreated (28,29). The patient's age, duration of symptoms, prior hospitalization, and platelet count have been identified as independent predictors of coronary artery abnormalities (21). In one study, predictors of IVIG resistance and coronary artery abnormalities in patients with KD were aspartase transaminase level of  $\geq 100$  IU/L, sodium level of  $\leq 133$  mmol/L, duration of illness before initial treatment of  $\leq 4$  days, neutrophil level of  $\geq 80\%$ , CRP level of  $\geq 10$  mg/dL, age of  $\leq 12$  months, and platelet count of  $\leq 30.0 \times 10^4/mm^3$  (20). We also analyzed the factors that may affect the duration of CALs, and the results indicated that female sex was a protective factor for the prognosis of CAL, while an overweight status, higher platelet count, lower albumin level and delayed IVIG treatment were independent risk factors for the prognosis of CAL. These findings are consistent with a previous report (9). However, the level of alanine transaminase and hemoglobin had no association with the duration of CAL. Additionally, the type of KD had no effect on the duration of CAL.

This study had several limitations. Firstly, this is a retrospective study, and all patients were from a single Pediatric Cardiac Clinic, which might have caused selection bias. Secondly, in our center, conventional or CT angiography is not performed routinely, therefore, comparison between echocardiography results and conventional or CT angiography findings can not be made. Finally, we did not use z score for assessment of CAL.

### Conclusion

Many children with KD developed CAL before IVIG treatment, and the duration of CAL was longer in children with an overweight status, low albumin level, high platelet count, and treatment later than 10 days after onset. Female sex was a protective factor for the prognosis of CAL, while an overweight status, high platelet count, and delayed IVIG treatment were independent risk factors for the prognosis of CAL.

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Figure legends

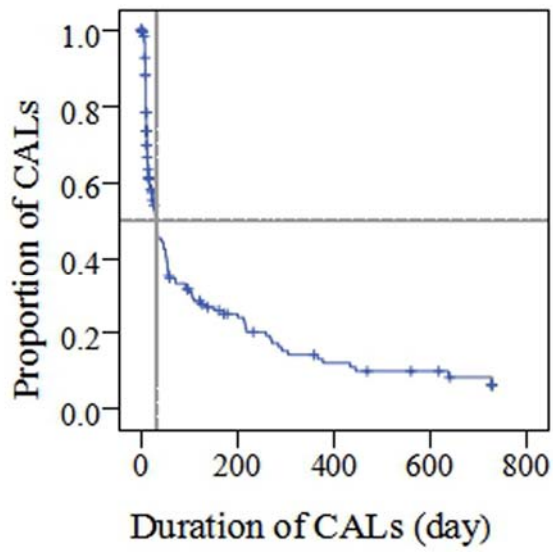


FIG. 1. Proportion of coronary artery lesions (CALs) at different time points.

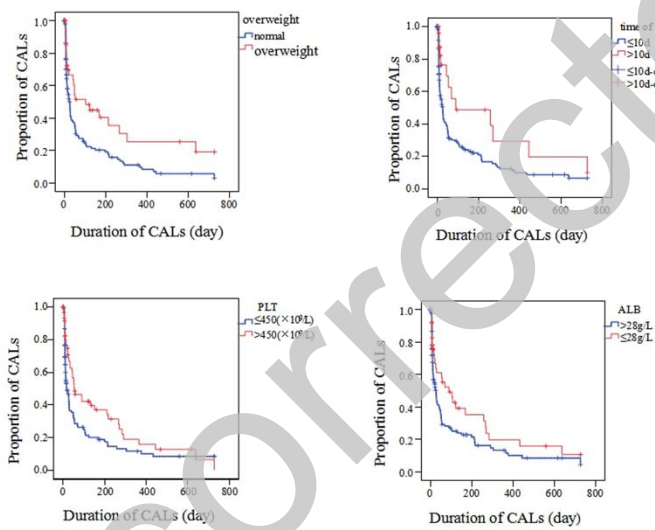


FIG. 2. Factors that affected the duration of coronary artery lesions (CALs).



**Table 1.** Baseline characteristics of patients who developed coronary artery lesions before intravenous immunoglobulin treatment

Characteristics	n (%)
<b>Age group (month)</b>	
≤36	152 (83.50)
>36	60 (6.90)
<b>Gender</b>	
Female	52 (28.6)
Male	130 (71.4)
<b>Overweight</b>	
Normal	140 (76.9)
Median+2s	42 (23.1)
<b>Type of Kawasaki disease</b>	
Complete	84 (46.2)
Incomplete	98 (53.8)
The number of signs	5.00 (5.00-6.00)
Polymorphous rash (yes, %)	115(63.2)
Bilateral conjunctival injection (yes, %)	157 (86.3)
Changes of the oral mucosa, lips and Tongue (yes, %)	162 (89.0)
Changes of extremities (yes, %)	106 (58.2)
Cervical lymphadenopathy (yes, %)	77(42.3)
Change of medical departments (yes, %)	24 (13.2)
Time of visiting doctor (days)	5 (4-7)
Day of illness on which IVIG was Given, median ( IQR )	7 (6-9)
Alanine transaminase >40IU/L	62 (34.2)
Platelet ≤450×10 <sup>9</sup> /L	122 (67)
C-reactive protein ≥150mg/L	33 (18.1)
Hemoglobin <100g/L	35 (19.2)
Intravenous immunoglobulin resistance (yes, %)	9 (4.9)

**Table 2.** Factors associated with resolution of coronary artery lesions before intravenous immunoglobulin treatment

Factors		cHR (95%CI)	aHR (95%CI)
Gender	Male	1	1
	Female	1.390 (0.953~2.028)	1.661 (1.117~2.470)
Overweight	No	1	1
	Yes	0.535 (0.345~0.830)	0.469 (0.298~0.737)
Type of Kawasaki disease	Complete KD	1	—
	Incomplete KD	0.853 (0.605~1.201)	—
Alanine transaminase (U/L)	<40	1	—
	>40	1.027 (0.716~1.473)	—
Platelet ( $\times 10^9/L$ )	$\leq 450$	1	1
	>450	0.663 (0.458~0.960)	0.649 (0.443~0.950)
Albumin (g/L)	>28	1	—
	$\leq 28$	0.657 (0.436~0.992)	—
Time of intravenous immunoglobulin treatment	$\leq 10d$	1	1
	>10d	0.508 (0.286~0.903)	0.392 (0.215~0.716)
Hemoglobin (g/L)	$\geq 100$	1	—
	<100	0.696 (0.440~1.102)	—