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ORIGINAL RESEARCH

Age-Stratified Risk Factors for Coronary Thrombosis in Kawasaki Disease Patients with Medium-to-Large Coronary Artery Aneurysms

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Objective: To identify risk factors for coronary thrombosis in Kawasaki disease (KD) patients with medium-to-large coronary artery aneurysms (CAA) (stratified by age at disease onset).

Methods: This retrospective study analyzed 490 consecutive KD patients with medium-to-large CAA treated at Children's Hospital of Chongqing Medical University. Demographic characteristics, initial treatment details, and follow-up echocardiographic data were collected. We divided KD patients into three categories according to age at disease onset: age <12 months, aged 12–47 months, and age >47 months. Multivariable logistic regression models were employed to assess coronary thrombosis risk factors in different age groups.

Results: Analysis showed the risk of coronary thrombosis by age after adjustment for confounders. In patients younger than 12 months, multiple coronary artery involvement and the left anterior descending artery (LAD) involvement was associated with coronary thrombosis. In KD patients older than 47 months, large CAA and multiple coronary artery involvement was associated with coronary thrombosis, In KD patients aged 12–47 months, male, intravenous immunoglobulin (IVIG) resistance, delayed IVIG initiation (>10 days post-fever onset), multiple coronary artery involvement and LAD involvement was associated with coronary thrombosis.

Conclusion: For KD with medium-to-large CAA, independent risk factors besides multiple coronary artery involvement are stratified by age. These findings underscore the importance of age-specific risk stratification to optimize thromboprophylaxis and long-term management.

Keywords: Kawasaki disease, age, coronary thrombosis, risk factors

Background

Kawasaki disease (KD) is an acute, immune-mediated systemic vasculitis that predominantly affects infants and young children under five years of age. The disease primarily targets medium-sized arteries, with particular involvement of the coronary arteries, and has emerged as the leading cause of acquired pediatric heart disease in developed countries.[1–3] The mainstay of KD treatment is intravenous immunoglobulin (IVIG), which significantly reduces the incidence of acute-phase coronary artery lesions. Despite timely treatment, approximately 6% of patients with KD still develop coronary artery aneurysms(CAA).[4] The pathogenesis involves persistent inflammatory cell infiltration affecting all three layers of the coronary arterial wall. Notably, endothelial dysfunction persists even after inflammation resolves, making patients more prone to coronary thrombosis and ischemic complications.[5,6] Consequently, the principal goals during the convalescent phase of KD management focus on thromboprophylaxis and minimizing cardiovascular risks.

Coronary thrombosis can block blood vessels and cause myocardial ischemia, which is a serious cardiovascular complication. At the long-term follow-up of KD, the majority of small CAA (85%) regressed to normal lumen with

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a good prognosis, whereas only a minority of large CAA (16%) regressed to normal lumen, this long-term abnormality in coronary artery structure increases the risk of coronary thrombosis.[7] An epidemiologic study from Japan demonstrated that coronary thrombosis occurred mainly in KD patients with medium-to-large CAA.[8] While the American Heart Association (AHA) guidelines recommend combined anticoagulation and antiplatelet therapy for thromboprophylaxis in these high-risk patients, this regimen does not completely eliminate the risk of coronary thrombosis.[9]

At present, the monitoring of coronary thrombosis mainly relies on regular follow-up, Unfortunately, optimal treatment opportunities are missed when coronary thrombosis is detected because children have poor language skills and can not accurately express relevant symptoms. During child development, both immune function and coronary artery diameter undergo dynamic changes. The immune-inflammatory response in KD exhibits age-related variations. Compared to older children, young children experience a more intense and prolonged vasculitis, characterized by more extensive endothelial damage, thereby elevating coronary thrombosis risk. Furthermore, age-related differences in coronary anatomy and hemodynamics contribute to this risk. The inherently smaller and more delicate coronary arteries in younger children provoke more pronounced flow disturbances and vortices. This flow stagnation facilitates the accumulation of platelets and clotting factors within the aneurysm, promoting coronary thrombosis.[9] Given the potential impact of age on thrombogenesis, we performed a systematic evaluation of age-stratified differences in coronary thrombosis risk among KD patients to better define critical periods for intervention.

Materials and Methods

Study Design and Patient Selection

This retrospective cohort study included patients who were diagnosed and treated at the Children's Hospital of Chongqing Medical University between January 2013 and December 2022. KD is characterized by persistent fever and non-response to antibiotics, with or without the following symptoms: chapped lips, hand and foot symptoms, cervical lymphadenopathy, rash, and bulbous conjunctival congestion.[9] Patients with consecutive KD who complicated with medium-to-large CAA in the acute phase were included in the study. Each patient was followed up for 2 years. Patients were excluded if they were lost to follow-up or had other severe disease affecting coronary artery, such as severe congenital heart disease or cardiomyopathy. All patients had complete data with no missing data. We divided KD patients into three categories according to age at disease onset: age <12 months, aged 12–47 months, and age >47 months. The Ethics Committee of Children's Hospital of Chongqing Medical University approved this study, and all subjects' guardians gave their informed consent.

Variables Collection

We have extracted demographics information and treatment information from the electronic medical record system, including age at onset of KD, sex, IVIG resistance, illness day of initial IVIG treatment. In addition, we also collected echocardiography data on the largest coronary artery diameter in the acute phase, including size of CAA, number of involved coronary arteries, left main coronary artery (LMCA) involvement, right coronary artery (RCA) involvement and left anterior descending artery (LAD) involvement. Size of CAA was primarily assessed by echocardiography and assigned a standardized Z score based on body surface area. Medium CAA was defined as: $5 \leq Z$ score < 10, and absolute dimension $<$ 8mm. Large CAA was defined as: Z score ≥ 10, or absolute dimension $\geq$ 8mm.[10] Coronary artery involvement was characterized by the presence of medium-to-large CAAs and their quantification in each affected artery. IVIG resistance was defined as the recurrence or persistence of fever within the first 36–48 hours after initial IVIG therapy. Illness day of initial IVIG treatment was recorded as the number of days from fever onset to the initiation of IVIG therapy.

In accordance with AHA guidelines, all patients were followed up with regular echocardiography in the outpatient. For the first month, follow-up was weekly; for the next 11 months, it was monthly; and after a year, it was every 3–6 months. We collected echocardiography at each follow-up, including the absolute diameters of LMCA, LAD and RCA, and assessed coronary thrombosis on the basis of the presence of echoes. Coronary thrombosis was the endpoint of this study during follow-up.

Statistical Analysis

All data were categorical variables, expressed as numbers (percentages), and were analyzed for statistically significant differences using the chi-square test. The logistic regression models were used to identify factors associated with coronary thrombosis in different age groups with odds ratios (OR) calculated with 95% confidence intervals after adjustment for confounders. All statistical analysis was performed using SPSS 26.0 software (SPSS, Inc., Chicago, USA). A 2-tailed P<0.05 was considered statistically.

Results

Patients' Characteristics

We analyzed 490 KD patients with medium-to-large CAA with a median age of 22 months (IQR, 8.0–40.8months). There were 179 patients younger than 12 months, 233 patients aged 12–47 months, and 78 patients older than 47 months. Among these, 156 patients developed coronary thrombosis.

Table 1 shows the characteristics of the patients at the onset of KD. There was no significant difference in sex, IVIG resistance, Illness day of initial IVIG treatment, Number of involved coronary arteries, RCA involvement and LAD involvement among different age groups. There was an association between coronary artery size and increasing age, with 25.7% (46 of 179) of patients with large CAA were younger than 12 months of age; 20.6% (48 of 233) were aged

Table 1 Characteristics of the Children Stratified by Patient Age at Onset of KD

Characteristic	Children, No. (%)				P value
	Total	Age at Onset of KD (month)			
		< 12 (N=179)	12–47 (N=233)	>47 (N=78)	
Sex					0.569
Male	326 (66.5)	114 (63.7)	160 (68.7)	52 (66.7)	
Female	164 (33.5)	65 (36.3)	73 (31.3)	26 (33.3)	
IVIG resistance					0.448
No	397 (81.0)	145 (81.0)	185 (79.4)	67 (85.9)	
Yes	93 (19.0)	34 (19.0)	48 (20.6)	11 (14.1)	
Illness day of initial IVIG treatment					0.900
≤ 10d	367 (74.9)	133 (74.3)	174 (74.7)	60 (76.9)	
>10d	123 (25.1)	46 (25.7)	59 (25.3)	18 (23.1)	
Size of CAA					0.025
Medium	368 (75.1)	133 (74.3)	185 (79.4)	50 (64.1)	
Large	122 (24.9)	46 (25.7)	48 (20.6)	28 (35.9)	
Number of involved coronary arteries					0.658
Single	236 (81.2)	91 (50.8)	108 (46.4)	37 (47.4)	
Multiple	254 (51.8)	88 (49.2)	125 (53.6)	41 (52.6)	
LMCA involvement					0.000
No	224 (45.7)	58 (32.4)	110 (47.2)	56 (71.8)	
Yes	266 (54.3)	121 (67.6)	123 (52.8)	22 (28.2)	
RCA involvement					0.145
No	65 (13.3)	27 (15.1)	33 (14.1)	5 (6.4)	
Yes	425 (86.7)	152 (84.9)	200 (85.9)	73 (93.6)	
LAD involvement					0.897
No	205 (41.8)	77 (43.0)	95 (40.8)	33 (42.3)	
Yes	285 (58.2)	102 (57.0)	138 (59.2)	45 (57.7)	
Coronary thrombosis					0.04
No	334 (68.2)	133 (74.3)	155 (66.5)	46 (59.0)	
Yes	156 (31.8)	46 (25.7)	78 (33.5)	32 (41.0)	

Abbreviations: KD, kawasaki disease; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; LMCA, left main coronary artery; RCA, right coronary artery; LAD, left anterior descending artery.

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between 12 and 47 months, and 35.9% (28 of 78) were older than 47 months, presenting a U-shaped distribution. The proportion of patients with LMCA involvement decreased with increasing age (<12 months, 121 of 179 [67.6%]; 12–47 months, 123 of 233 [52.8%]; and >47 months, 22 of 78 [28.2%]). The proportion of patients with coronary thrombosis increased with increasing age (<12 months, 46 of 179 [25.7%]; 12–47 months, 78 of 233 [33.5%]; and >47 months, 32 of 78 [41.0%]).

Incidence of Coronary Thrombosis in Different Age

As shown in Figure 1, age is a risk factor for coronary thrombosis, with the OR were 1.455 (0.945–2.241) among patients aged between 12 and 47 months, and the OR were 2.011 (1.146–3.529) among those older than 47 months (reference: younger than 12 months group).

Risk Factors Associated with Coronary Thrombosis

Tables 2 and 3 showed univariate and multivariable ORs of coronary thrombosis in the age groups of KD patients. In patients younger than 12 months, sex, illness day of initial IVIG treatment, size of CAA, number of involved coronary arteries, LMCA involvement and LAD involvement was associated with coronary thrombosis. Multivariable logistic regression analysis revealed that multiple coronary artery involvement (OR 8.16; 95% CI 2.84–23.16; P<0.001) and LAD involvement (OR 5.57; 95% CI 1.75–17.72; P=0.004) were independently associated with coronary thrombosis. In KD patients aged 12–47 months, sex, IVIG resistance, illness day of initial IVIG treatment, size of CAA, number of involved coronary arteries, LMCA involvement and LAD involvement was associated with coronary thrombosis. Multivariable logistic regression analysis revealed that male (OR 3.05; 95% CI 1.36–6.82; P=0.007), IVIG resistance (OR 2.80; 95% CI 1.22–6.43; P=0.015), delayed IVIG initiation (>10 days post-fever onset) (OR 2.17; 95% CI 1.02–4.62; P=0.044), multiple coronary artery involvement (OR 4.69; 95% CI 2.14–10.25; P<0.001) and LAD involvement (OR 3.16; 95% CI 1.42–7.02; P=0.005) were independently associated with coronary thrombosis. In KD patients older than 47 months, size of CAA, number of involved coronary arteries, LMCA involvement and LAD involvement was associated with coronary thrombosis. Multivariable logistic regression analysis revealed that large CAA (OR 7.87; 95% CI 2.30–26.94; P=0.001) and multiple coronary artery involvement (OR 6.30; 95% CI 1.80–22.06; P=0.004) were independently associated with coronary thrombosis.

Discussion

In this study, we confirmed that older children have a higher risk of coronary thrombosis than younger children when stratified by age. We also found the different risk of coronary thrombosis in different age after adjustment for confounders: In patients younger than 12 months, multiple coronary artery involvement and LAD involvement was associated with coronary thrombosis, In KD patients older than 47 months, large CAA and multiple coronary artery

Patient age (month)	OR(95%CI)
<12	1 (Reference)
12–47	1.455 (0.945-2.241)
>47	2.011 (1.146-3.529)

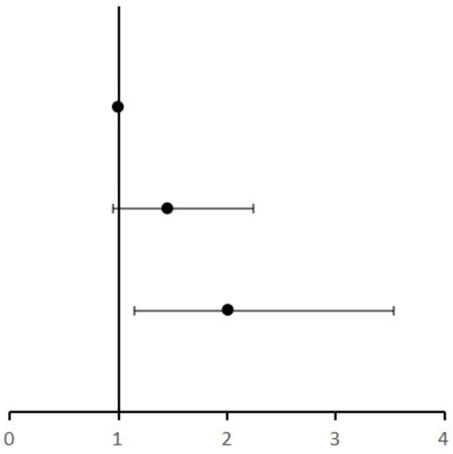

Figure 1 Risk of coronary thrombosis in different age.

Table 2 Univariate Analysis of Coronary Thrombosis Stratified by 3 Categories of Patient Age at Onset of KD

Characteristic	Children					
	Age at Onset of KD (month)					
	< 12 (N=179)		12–47 (N=233)		>47 (N=78)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex		0.045		0.001		0.516
Female	Reference		Reference		Reference	
Male	2.18 (1.02–4.05)		3.16 (1.60–6.22)		0.73 (0.28–1.89)	
IVIG resistance		0.582		0.044		0.748
No	Reference		Reference		Reference	
Yes	1.26 (0.55–2.89)		1.95 (1.02–3.73)		1.24 (0.34–4.46)	
Illness day of initial IVIG treatment		0.017		0.009		0.158
≤ 10d	Reference		Reference		Reference	
>10d	2.41 (1.17–4.97)		2.24 (1.22–4.11)		2.16 (0.74–6.28)	
Size of CAA		<0.001		<0.001		<0.001
Medium	Reference		Reference		Reference	
Large	4.16 (2.01–8.62)		3.38 (1.76–6.50)		14.67 (4.70–45.77)	
Number of involved coronary arteries		<0.001		<0.001		<0.001
Single	Reference		Reference		Reference	
Multiple	15.00 (5.55–40.55)		8.95 (4.67–17.98)		12.34 (3.94–38.69)	
LMCA involvement		0.005		<0.001		<0.001
No	Reference		Reference		Reference	
Yes	3.47 (1.44–8.33)		3.06 (1.71–5.47)		13.50 (3.90–46.69)	
RCA involvement		0.358		0.417		0.054
No	Reference		Reference		–	
Yes	1.63 (0.58–4.58)		1.41 (0.62–3.19)		–	
LAD involvement		<0.001		<0.001		0.001
No	Reference		Reference		Reference	
Yes	12.77 (4.33–37.65)		6.34 (3.18–12.66)		6.16 (2.13–17.85)	

Abbreviations: KD, kawasaki disease; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; LMCA, left main coronary artery; RCA, right coronary artery; LAD, left anterior descending artery.

Table 3 Multivariable Analysis of Coronary Thrombosis Stratified by 3 Categories of Patient Age at Onset of KD

Characteristic	Age at Onset of KD					
	< 12 Month		12–47 Month		>47 Month	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (Male)	NA		3.05 (1.36–6.82)	0.007		
IVIG resistance (Yes)			2.80 (1.22–6.43)	0.015		
Illness day of initial IVIG treatment (>10d)	NA		2.17 (1.02–4.62)	0.044		
Size of CAA (Large)	NA		NA		7.87 (2.30–26.94)	0.001
Number of involved coronary arteries (Multiple)	8.16 (2.84–23.16)	<0.001	4.69 (2.14–10.25)	<0.001	6.30 (1.80–22.06)	0.004
LMCA involvement (Yes)	NA		1.91 (0.97–3.79)	0.063	NA	
RCA involvement (Yes)						
LAD involvement (Yes)	5.57 (1.75–17.72)	0.004	3.16 (1.42–7.02)	0.005	NA	

Abbreviations: KD, kawasaki disease; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; LMCA, left main coronary artery; RCA, right coronary artery; LAD, left anterior descending artery.

involvement was associated with coronary thrombosis, In KD patients aged 12–47 months, male, IVIG resistance, delayed IVIG initiation (>10 days post-fever onset), multiple coronary artery involvement and LAD involvement was associated with coronary thrombosis.

KD is an acute systemic vasculitis triggered by immune dysregulation.[11] The ensuing inflammatory infiltration directly damages the vascular wall, leading to endothelial destruction and the rupture of elastin fibers and the muscular layer, this elevated risk of coronary complications. Furthermore, an exuberant inflammatory burden can exceed the neutralizing capacity of intravenous immunoglobulin (IVIG), thereby increasing the likelihood of treatment resistance.[9]

Multiple coronary artery involvement is an independent risk factor for coronary thrombosis in each age group, and we suspect that inflammation-induced vessel wall damage is more severe in patients with multiple coronary artery involvement than in those with single coronary artery involvement, as a result, more patients with multiple coronary artery involvement experience coronary thrombosis. Peng Y found that the number of involved coronary arteries were major factors in coronary thrombosis in KD patients, which is consistent with our results.[12]

Large CAA have been identified as a risk factor for coronary thrombosis in previous studies.[12] In our study, although large CAA were associated with coronary thrombosis in univariate logistic regression analysis in each age group, only patients older than 47 months were associated with coronary thrombosis after adjusting for confounders, this may be related to the absolute diameter of the large CAA. Coronary artery diameter is greater in older patients compared with younger patients, and therefore, for older patients presenting with large CAA, the absolute diameter is greater and the retraction rate is relatively lower, suggesting that larger coronary aneurysms are more likely to occur in older patients. Previous studies have also shown that large CAA with the large absolute diameter are more likely to develop coronary thrombosis.[13]

Coronary thrombosis is closely related to platelet activation, the low shear stress environment and flow stasis.[14,15] LAD is the apex of the left main branch of the coronary artery, extending downward from the anterior interventricular groove, which has fast blood flow and low shear stress, and is prone to stenosis and thrombosis. LAD is the most common site of coronary atherosclerosis in adults.[16] In our study, LAD were the risk factor in patients younger than 47 months but not in patients older than 48 months, which may be associated with coronary hypoplasia in younger children.

There were still some limitations in this study. For instance, this was a retrospective study, and there may be selection bias. In addition, this study was a single-center study with a large number of cases but limited generalizability. Finally, because coronary thrombosis was primarily assessed by echocardiography in this study, there are some limitations to echocardiography imaging in detecting distal coronary arteries.

Conclusions

This cohort study reveals age-specific variations in risk factors for coronary thrombosis among KD patients with medium-to-large CAA. While multiple coronary involvement consistently emerged as a significant risk factor across all age groups, our findings demonstrate that other independent risk factors for coronary thrombosis exhibit distinct patterns at different stages of patient development. These results underscore the critical importance of age-stratified risk assessment in the management of KD patients with medium-to-large CAA. To optimize long-term outcomes, we recommend implementing age-tailored prevention strategies and developing individualized surveillance protocols based on these risk factor profiles.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval for this study was obtained from the Ethics Committee of the Chongqing Medical University Children's Hospital.

Consent for Publication

Informed consent was obtained from the guardians of all patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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