Association Between Clinical Risk Factors and Coronary Artery Lesions in Children with Kawasaki Disease

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Abstract

Background: Kawasaki disease (KD) is one of the leading causes of acquired coronary artery diseases in childhood. In KD patients, the evidence on the association between easy-to-assess clinical risk factors and development of coronary artery lesion (CAL). Our study aimed to determine the clinical biomarkers that were associated with latent occurrence of CAL in pediatric patients with KD.

Methods: 260 pediatric KD patients were recruited. The outcome of our study is CAL, including coronary dilation, coronary aneurysm, and intimal thickening of coronary arteries. Data of general information, medical history, results of laboratory examinations and echocardiography data were collected. Logistic regression method was carried out to explore the associations between biomarkers and each CAL.

Results: Sixty-six (25.4 %), thirty-nine (15 %) and fifty-six patients (21.5 %) of the participants had coronary dilation, coronary aneurysm, and intimal thickening of coronary arteries, respectively. Single-variable analysis found age, gender, duration of fever, time of initial use of IVIG, ESR, WBC, time of platelet increase, maximum value of platelet, albumin and IgG level were associated with CAL. In multivariable logistic analysis, younger in age and male were associated with all three outcomes of CAL. Lower serum albumin level and later initial use of IVIG were linked to higher risk of coronary dilation and coronary aneurysm.

Conclusion: In a Chinese pediatric population of KD, younger in age, male, lower serum albumin level, and later initial use of IVIG were risk factors of CAL. Our findings had high practicability to be implemented in clinical practice, however, is to be verified by future studies.

Background

Kawasaki disease (KD), also called mucocutaneous lymph node syndrome, is an acute, febrile vasculitis disorder which is one of the leading causes of acquired coronary artery diseases in childhood, especially in pediatric patients younger than five years.

The epidemiology of KD varies greatly by geographic location. In western countries, the annual incidence of KD for children under five years old ranged from 4 to 25 per 100000 [1–3]. Nevertheless, the incidence of KD was higher among north and east Asians. For example, in Japan, the accordingly incidence in children under 5 was 243.1 per 100 000 in 2011, and 264.8 per 100000 in 2012 [4]. In China, the annual incidence ranged from 5 to 69 per 100000 [5–8]. Meanwhile, the incidence in Asian area was on increase [8–10]. Besides regional difference, the higher incidence in Japanese children was also linked to the ethnic variation. It was reported that among all ethnic groups in children under 5 years old in Hawaii, children of Japanese descent had the highest incidence (210.5 per 100 000), while Caucasian children had the lowest (13.7 per 100 000) [11]. The above-mentioned evidence highlighted the importance of relevant studies in Asian countries.

KD is one of the most common causes of acquired heart disease in children worldwide [9], furthermore, it is a condition with potential life-long health affect [12]. The long-term prognosis is determined by the level of coronary artery lesion (CAL) [13]. For instance, Japanese studies reported that the standardized mortality ratios in KD patients with cardiac sequelae, for example coronary artery aneurysms, were higher than those without [14, 15]. Moreover, in KD patients with coronary artery aneurysms and stenoses, sudden death of myocardial infarction (MI) can occur many years later in childhood and even in adulthood [16]. Therefore, for the purpose of giving effective and targeted treatment which could possibly have life-long benefits, it is important to recognize patients who are at elevated risk with CAL in the early stage of KD. Determine easy-to-assess clinical characteristics and biomarkers, which were

associated with the progression of CAL, could help pediatrician provide timely preventive and therapeutic measures to reduce the prevalence of CAL. Clinical characteristics and biomarkers such as laboratory findings are useful in supporting a diagnosis of KD [17], however, the evidence on the association between them and development of CAL in pediatric KD patients are lacking.

Given the scarce findings and the clinical importance on clinical risk factors CAL in KD patients, we conducted the current study, aiming to determine the clinical biomarkers that were associated with latent occurrence of CAL in pediatric patients with KD. Multiple outcomes (coronary dilation, coronary aneurysm, and intimal thickening of coronary arteries) were involved in our study, to provide more comprehensive evidence on the topic.

Methods

Participants

We investigated pediatric patients with complete KD who were admitted at the Department of Cardiology in Guangzhou Women's and Children's Medical Center from June to December 2017. The inclusion criteria for our study were: (1) patients that were diagnosed as complete KD for the first time, (2) patients that had complete data on general information, biomarkers, and outcome factors, and (3) the legal guardian of the patient gave informed consent to take part in the study. Patients did not have insufficient evidence to be diagnosed as KD, with incomplete KD, in recurrent episode of KD, and those did not have complete data were excluded from our study. Based on these inclusion criteria, a total of 260 subjects were included. According to Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young by American Heart Association [18], our diagnostic criteria for complete KD was based on 5 principal clinical features, namely conjunctival injection, rash, strawberry tongue or red lips, neck lymphadenopathy, and edema and erythema of the hand and foot. Children were diagnosed as complete KD if they had 4 or 5 of these aforementioned symptoms, with fever that lasted for 5 or more days. Incomplete KD were diagnosed as 2 or there of the symptoms with fever for 5 or more days.

Outcome

The outcome of our study is CAL, including coronary dilation, coronary aneurysm, and intimal thickening of coronary arteries. According to Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association (2017) [19], the coronary dilation and coronary aneurysm were diagnosed and classified based on Z values: (1) No involvement: always <2 , (2) Dilation only: 2 to <2.5 ; or if initially <2 , a decrease in Z score during follow-up ≥ 1 , (3) Small aneurysm: ≥ 2.5 to <5 , (4) Medium aneurysm: ≥ 5 to <10 , and absolute dimension <8 mm, and (5) Large or giant aneurysm: ≥ 10 , or absolute dimension ≥ 8 mm. Intimal thickening of coronary arteries were assessed with optical coherence tomography. Data on incidence, severity and location of each CAL were collected and included into the analysis.

Data collection

Data of the recruited patients were extracted from medical records of Hospital Information System, which included the patient's general information, history of present illness, results of laboratory examinations, echocardiography data and history of medication usage. The laboratory examinations were measured upon admission. Intravenous immunoglobulin (IVIG) resistance was defined as a body temperature of $\geq 38.0^{\circ}\text{C}$ that lasted between 36 hours and 7 days, or recurrence of fever after the completion of IVIG infusion [19].

Ethics

The protocol of the present study was reviewed and approved by the Guangzhou Women and Children Medical Center Ethics Committee (2021241A01) and was conducted according to the International Ethical Guidelines for Research Involving Human Subjects stated in the Declaration of Helsinki. The children's families provide written informed consent.

Statistical analysis

Data were described as the mean and standard deviation (SD) for continuous variables, and number and percentages for categorical variables. Continuous variables were compared using t-tests to estimate the significance of differences between patients with and without certain CAL. Categorical variables were compared using χ^2 tests. Potential predictors were selected for each CAL separately. Variables presented statistically significance for at least one outcome were included in the multivariable logistic regression models. Logistic regression was carried out to explore the associations between potential risk factors and each CAL. Multivariable logistic models were established to identify the risk factors. A sensitivity analysis was carried out by adding the variable "whether had IVIG resistance" into the final models, to explore whether IVIG resistance had modification effect of the relationships that were found in the main analysis. Statistical analyses were performed using STATA software, p values that <0.05 were considered statistically significant.

Results

General information of the participants

In total, 260 patients with infantile KD were recruited in our study, with a mean age of 24.05 month (SD = 21.85 month), and a ratio of gender (male: female) as 172:88. The mean duration of fever was 7.52 days (SD = 3.27 days). The mean time of initial use of IVIG was 6.44 days (SD = 2.12 days) after the onset of KD. Eighty-four percent of the participants used IVIG 1 time (n = 218), and 3 (1.2%) of the total sample never used IVIG. Twenty-four children had IVIG resistance, accounted for 9.2% of the total participants. The detailed general information is displayed in Table 1.

Table 1
Description of general characteristics

Characteristics	Mean (SD)/n (%)
Age (month)	24.05 (21.85)
Gender	
Male	172 (66.2%)
Female	88 (33.9%)
Blood type	
A	76 (29.2%)
B	67 (25.8%)
O	108 (41.5%)
AB	9 (3.5%)
Duration of fever (day)	7.52 (3.27)
Time of initial use of IVIG	6.44 (2.12)
Frequency of IVIG usage (time)	1.15 (0.43)
0	3 (1.2%)
1	218 (83.9%)
2	35 (13.5%)
3	4 (1.5%)
IVIG resistance	24 (9.23%)
IVIG: intravenous immunoglobulin; SD: standard deviation	

Description of coronary artery lesion

Prevalence of CALs is displayed in Table 2. Sixty-six (25.4%) of the participants had coronary dilation, with a mean time of first occurrence of 34.31 days (SD = 70.34 days) after the onset of KD. In 34 (53.1%) patients, coronary dilation located only in left coronary arteries. Thirty-nine (15%) of the participants suffered from coronary aneurysm, with a mean time of first occurrence of 11.73 days (SD = 6.34 days) after the onset of KD. In 22 (56.4%) patients, the coronary aneurysm located in both left and right coronary arteries. Most of the patients had coronary aneurysm of small size (84.6%), and 4/1/1 patients that had medium/large/extra-large coronary aneurysm, respectively. The mean time of regression of coronary aneurysm was 50.13 days (SD = 63.63 days) after the onset of KD. Fifty-six patients (21.5%) had intimal thickening of coronary arteries. Most participants had intimal thickening only in left coronary arteries, which is similar to coronary dilation. One patient had thrombus. The mean time of total recovery was 81.27 days (SD = 261 days).

Table 2
Description of coronary artery lesion

Status of coronary artery lesion	Mean (SD)/n (%)
Coronary aneurysm	39 (15%)
Time of occurrence of coronary aneurysm (day after the onsite of KD)	11.71 (6.34)
Size of coronary aneurysm	
Small	33 (84.6%)
Medium	4 (10.3%)
Large	1 (2.6%)
Extra large	1 (2.6%)
Location of coronary aneurysm	
Left only	12 (30.8%)
Right only	5 (12.8%)
Left and right	22 (56.4%)
Coronary aneurysm regression time (day after the onsite of KD)	50.13 (63.63)
Thrombus	1 (0.4%)
Coronary dilation	66 (25.4%)
Time of occurrence of coronary dilation (day after the onsite of KD)	34.31 (70.34)
Location of coronary dilation	
Left only	34 (53.1%)
Right only	5 (7.8%)
Left and right	25 (39.1%)
Intimal thickening	56 (21.5%)
Location of coronary intimal thickening	
Left only	27 (48.2%)
Right only	7 (12.5%)
Left and right	22 (39.3%)
Time of recovery (day after the onsite of KD)	81.27 (261.95)
SD: standard deviation	

Comparison of clinical biomarkers between participants with and without CAL

Duration of fever, and time of initial usage of IGIV were positively correlated with the incidence of all the three CALs, while month of age and serum albumin level were negatively correlated. Gender was associated only with coronary dilation, the percentage of boys in those with coronary dilation was higher than without (78.8% v.s. 61.9%, $p = 0.012$).

Erythrocyte sedimentation rate (ESR) was positively linked to only coronary aneurysm. White blood cell count (WBC) was positively related to coronary aneurysm and intimal thickening. Time of the increase in platelets was negatively correlated with coronary dilation, and the maximum value of platelets was positively related to coronary dilation and coronary aneurysm. IgG level was only positively related to intimal thickening. Results of the comparison of clinical biomarkers between participants with and without CAL are displayed in Table 3.

Table 3
Comparison of clinical biomarkers between participants with and without CAL

Potential Risk Factors	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value
	CD	Non-CD		CA	Non-CA		CIT	Non-CIT	
Age	17.5 (16.63)	26.27 (22.98)	0.005*	14.82 (15.99)	25.67 (22.37)	0.004*	15.93 (14.61)	26.27 (22.98)	0.002*
Gender									
Male	52 (78.8%)	120 (61.9%)	0.012*	30 (76.9%)	142 (64.3%)	0.123	43 (76.8%)	129 (63.2%)	0.058
Female	14 (21.2%)	74 (38.1%)		9 (23.1%)	79 (35.7%)		13 (23.2%)	75 (36.8%)	
Blood type									
A	18 (27.3%)	58 (29.9%)	0.968	9 (23.1%)	67 (30.3%)	0.703	12 (21.4%)	64 (31.4%)	0.450
B	18 (27.3%)	49 (25.3%)		12 (30.8%)	55 (24.9%)		18 (32.1%)	49 (24%)	
O	28 (42.4%)	80 (41.2%)		16 (41%)	92 (41.6%)		24 (42.9%)	84 (41.2%)	
AB	2 (3%)	7 (3.6%)		2 (5.1%)	7 (3.2%)		2 (3.6%)	7 (3.4%)	
Duration of fever (day)	8.53 (3.8)	7.18 (2.99)	0.004*	9.56 (4.84)	7.16 (2.76)	<0.001*	8.8 (3.98)	7.17 (2.95)	0.001*
Time of initial use of IVIG (day after the onsite of KD)	7.22 (2.55)	6.17 (1.89)	0.001*	7.77 (3.44)	6.2 (1.69)	<0.001*	7.22 (2.51)	6.22 (1.96)	0.002*
ESR (mm/h)	38.26 (24.92)	36.77 (19.72)	0.622	43.36 (25.32)	36.05 (20.16)	0.046*	37.96 (24.79)	36.92 (20.06)	0.745
hsCRP (mg/L)	119.96 (167.4)	95.13 (91.94)	0.133	134.76 (157.57)	95.55 (106.36)	0.051	93.81 (65.95)	103.52 (126.33)	0.580
WBC count ($\times 10^9/L$)	18.49 (6.5)	16.98 (5.5)	0.067	20.9 (6.21)	16.74 (5.5)	<0.001*	18.86 (6.61)	16.95 (5.5)	0.029*
HB (g/L)	104.15 (112.47)	98.43 (11)	0.484	87.54 (11.64)	102.06 (61.61)	0.144	90.8 (11.72)	102.38 (64.09)	0.180

*p<0.05.

ALT: alanine aminotransferase; CA: Coronary aneurysm; CD: Coronary dilation; CIT: Coronary intimal thickening; CK-MB: creatine kinase isoenzyme; DBil: direct bilirubin; ESR: erythrocyte sedimentation rate; HB: hemoglobin; hsCRP: hypersensitive C-reactive protein; IBil: indirect bilirubin; IVIG: intravenous immunoglobulin; LDH: lactic dehydrogenase; PLT: platelet; SD: Standard deviation; TBA: total bile acid; TBil: total bilirubin; WBC: white blood cell count

Potential Risk Factors	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value
	CD	Non-CD		CA	Non-CA		CIT	Non-CIT	
Time of PLT increase (day after the onsite of KD)	83.27 (264.2)	207.02 (398.3)	0.019*	85.28 (267.23)	191.55 (386.25)	0.100*	114.46 (309.2)	192.39 (386.88)	0.166
Maximum PLT	679.41 (190.08)	580.72 (193.41)	<0.001*	709.85 (198.81)	587.4 (191.28)	<0.001*	650.95 (192.75)	593.37 (196.76)	0.053
Albumin (g/L)	34.93 (4.66)	36.68 (4.36)	0.006*	33.95 (5.03)	36.65 (4.28)	<0.001*	35.03 (4.78)	36.57 (4.37)	0.024*
ALT (U/L)	74.03 (133.05)	68.16 (142.15)	0.769	67.3 (74.92)	70.06 (148.3)	0.909	65.76 (79.76)	70.72 (152.18)	0.815
TBil (μmol/L)	7.63 (12.34)	8.19 (12.28)	0.751	7.54 (14.06)	8.14 (11.96)	0.779	7.34 (12.05)	8.24 (12.36)	0.630
DBil (μmol/L)	4.55 (10.3)	4.77 (10.48)	0.886	4.6 (12.04)	4.73 (10.13)	0.943	4.31 (10.23)	4.82 (10.48)	0.744
IBil (μmol/L)	6.31 (26)	3.41 (2.64)	0.128	2.94 (2.24)	4.35 (14.33)	0.539	3.03 (2.26)	4.44 (14.87)	0.486
TBA (μmol/L)	13.69 (37.28)	16.79 (33.63)	0.540	11.92 (15.59)	16.78 (36.87)	0.419	10.29 (14.22)	17.54 (37.96)	0.174
IgG (g/L)	9.58 (8.03)	8.14 (5.48)	0.105	9.43 (8.46)	8.34 (5.78)	0.317	10.16 (9.87)	8.05 (4.73)	0.025*
IgA (g/L)	0.74 (0.57)	0.72 (0.58)	0.855	0.74 (0.64)	0.72 (0.56)	0.839	0.66 (0.45)	0.74 (0.61)	0.310
IgM (g/L)	1.06 (0.54)	1.16 (0.53)	0.213	1 (0.57)	1.16 (0.53)	0.095	1.05 (0.59)	1.16 (0.52)	0.188
IgE (IU/mL)	100.06 (172.21)	174.79 (371.48)	0.116	85.69 (126.48)	168.2 (356.77)	0.155	87.5 (133.82)	174.58 (368.18)	0.084
LDH (U/L)	275.62 (94.07)	273.71 (82.87)	0.876	253 (44.62)	277.84 (90.46)	0.099	273.07 (105.11)	274.5 (79.94)	0.913
CK-MB (U/L)	19.26 (12.09)	23.02 (32.72)	0.362	17.84 (6.82)	22.79 (31.13)	0.331	23.55 (33.72)	21.67 (27.56)	0.670
*p<0.05.									
ALT: alanine aminotransferase; CA: Coronary aneurysm; CD: Coronary dilation; CIT: Coronary intimal thickening; CK-MB: creatine kinase isoenzyme; DBil: direct bilirubin; ESR: erythrocyte sedimentation rate; HB: hemoglobin; hsCRP: hypersensitive C-reactive protein; IBil: indirect bilirubin; IVIG: intravenous immunoglobulin; LDH: lactic dehydrogenase; PLT: platelet; SD: Standard deviation; TBA: total bile acid; TBil: total bilirubin; WBC: white blood cell count									

Multivariable analyses

In the main analysis (Table 4), age (OR = 0.975, 95% CI: 0.955 to 0.994, P value = 0.012), being female (OR = 0.304, 95% CI: 0.142 to 0.648, P value = 0.002) and serum albumin level (OR = 0.926, 95% CI: 0.858 to 0.998, p value = 0.045) were found to be negatively linked with the risk of coronary dilation, while time of initial use of IVIG (OR = 1.255, 95%

CI: 1.047 to 1.503, p value = 0.014) was positively linked. Age (OR = 0.962, 95% CI: 0.933 to 0.991, P value = 0.012) and serum albumin level (OR = 0.890, 95% CI: 0.809 to 0.979, p value = 0.017) were found to be negatively linked with the risk of coronary aneurysm, while WBC (OR = 1.088, 95% CI: 1.012 to 1.169, p value = 0.023) and time of initial use of IVIG (OR = 1.214, 95% CI: 1.003 to 1.469, p value = 0.047) were positively linked. For the outcome as intimal thickening, age (OR = 0.960, 95% CI: 0.936 to 0.984, P value = 0.001), being female (OR = 0.409, 95% CI: 0.188 to 0.889, p value = 0.024) were negatively associated with the risk.

Table 4
Result from multi-variable logistic regression

Potential Risk Factors	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value
	CD	Non-CD		CA	Non-CA		CIT	Non-CIT	
Age (month)	0.975	(0.955, 0.994)	0.012*	0.962	(0.933, 0.991)	0.012*	0.960	(0.936, 0.984)	0.001*
Gender (Female compared to male)	0.304	(0.142, 0.648)	0.002*	0.483	(0.195, 1.195)	0.116	0.409	(0.188, 0.889)	0.024*
Duration of fever (day)	0.962	(0.836, 1.107)	0.586	1.128	(0.975, 1.306)	0.106	1.015	(0.893, 1.153)	0.818
Time of initial use of IVIG (day after the onsite of KD)	1.255	(1.047, 1.503)	0.014*	1.214	(1.003, 1.469)	0.047*	1.184	(1.000, 1.401)	0.050
ESR (mm/h)	1.006	(0.991, 1.021)	0.438	1.017	(0.999, 1.036)	0.067	1.007	(0.991, 1.022)	0.395
WBC count ($\times 10^9/L$)	1.007	(0.949, 1.067)	0.828	1.088	(1.012, 1.169)	0.023*	1.030	(0.969, 1.095)	0.336
Time of PLT increase (day after the onsite of KD)	0.999	(0.998, 1.000)	0.210	1.000	(0.999, 1.002)	0.753	0.999	(0.998, 1.001)	0.341
Maximum PLT count ($\times 10^9/L$)	1.001	(0.999, 1.003)	0.298	1.000	(0.998, 1.002)	0.980	0.999	(0.997, 1.001)	0.464
Albumin (g/L)	0.926	(0.858, 0.998)	0.045*	0.890	(0.809, 0.979)	0.017*	0.927	(0.857, 1.002)	0.056
IgG (g/L)	1.027	(0.971, 1.086)	0.351	0.993	(0.932, 1.059)	0.832	1.035	(0.976, 1.097)	0.256
*p<0.05.									
CA: Coronary aneurysm; CD: Coronary dilation; CIT: Coronary intimal thickening; ESR: erythrocyte sedimentation rate; LDH: lactic dehydrogenase; PLT: platelet; SD: Standard deviation; WBC: white blood cell									

In the sensitivity analysis that added IVIG resistance as a covariance in each model (Table 5), the risk factors for coronary dilation and intimal thickening remained the same. Time of initial use of IVIG and WBC for coronary aneurysm became statistically insignificant.

Table 5
Result from sensitivity analysis

Potential Risk Factors	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value	Mean (SD)/n (%)		p value
	CD	Non-CD		CA	Non-CA		CIT	Non-CIT	
IVIG resistance	1.217	(0.354, 4.188)	0.755	0.474	(0.085, 2.637)	0.394	0.491	(0.113, 2.134)	0.342
Age (month)	0.975	(0.956, 0.995)	0.014*	0.959	(0.93, 0.990)	0.009*	0.958	(0.934, 0.983)	0.001*
Gender (Female compared to male)	0.304	(0.143, 0.648)	0.002*	0.469	(0.188, 1.168)	0.104	0.402	(0.184, 0.878)	0.022*
Duration of fever (day)	0.952	(0.815, 1.113)	0.538	1.163	(0.988, 1.369)	0.070	1.047	(0.910, 1.206)	0.518
Time of initial use of IVIG (day after the onsite of KD)	1.270	(1.041, 1.550)	0.018*	1.172	(0.953, 1.441)	0.133	1.140	(0.949, 1.369)	0.160
ESR (mm/h)	1.006	(0.991, 1.021)	0.456	1.018	(1.000, 1.037)	0.053	1.008	(0.992, 1.023)	0.339
WBC count ($\times 10^9/L$)	1.006	(0.949, 1.067)	0.844	1.094	(1.016, 1.179)	0.017*	1.034	(0.972, 1.100)	0.291
Time of PLT increase (day after the onsite of KD)	0.999	(0.998, 1.001)	0.218	1.000	(0.999, 1.002)	0.812	0.999	(0.998, 1.001)	0.310
Maximum PLT count ($\times 10^9/L$)	1.001	(0.999, 1.003)	0.298	1.000	(0.997, 1.002)	0.952	0.999	(0.997, 1.001)	0.463
Albumin (g/L)	0.925	(0.858, 0.998)	0.044*	0.890	(0.809, 0.980)	0.018	0.928	(0.857, 1.003)	0.061
IgG (g/L)	1.026	(0.970, 1.085)	0.376	0.999	(0.936, 1.065)	0.969	1.039	(0.980, 1.102)	0.202
*p<0.05.									
CA: Coronary aneurysm; CD: Coronary dilation; CIT: Coronary intimal thickening; ESR: erythrocyte sedimentation rate; IVIG: intravenous immunoglobulin; LDH: lactic dehydrogenase; PLT: platelet; SD: Standard deviation; WBC: white blood cell									

Discussion

In total, 260 patients with infantile KD were recruited in our study, with a mean age of 24 month. Sixty-six (25.4%), thirty-nine (15%) and fifty-six patients (21.5%) of the participants had coronary dilation, coronary aneurysm, and intimal thickening of coronary arteries, respectively. Single-variable analysis found age, gender, duration of fever, time of initial use of IVIG, ESR, WBC, time of platelet increase, maximum value of platelet, albumin and IgG level were associated with CAL. In multi-variable logistic analysis, younger in age, male, lower serum albumin level, and later initial use of IVIG were found to be potential risk factors of CAL in the studied population. In the sensitivity analysis that added IVIG resistance as a covariance in the models, the risk factors for coronary dilation and intimal thickening remained the same.

There are few studies that explored the association between biomarkers and CAL in KD patients. A number of them found similar results to our study, suggested that lower albumin was a risk factor of CAL in KD patients [20, 21]. Meanwhile, other risk factors have also been revealed in the current literature, such as hemoglobin, fever duration, C-reactive protein, and so on. For instance, H.J. Kim et al reported that compared to KD patients without CAL, those with CAL had significantly higher serum interleukin-6 levels (228.26 ng/mL vs. 39.18 ng/mL), and lower body mass index (15.09 vs. 16.60) [22]. Li et al. revealed that red blood cell distribution width could be used as an independent predictor of CAL in KD patients [23]. Shao et al. found Apo-A level, as a predictor of CAL in KD patients, was significantly negatively linked to CAL [24]. In our study, factors such as duration of fever and platelet level were not found to be significantly associated with CAL. The variance in ethnicity, geographic location and seasonality could partially explain the divergences in our findings. In addition, a large body of evidence involved research on potential predictive biomarkers of CAL in KD patients, which were novelty but could not be easily measured and monitored in the general medical practice. The biomarkers included adropin [20], plasminogen activator inhibitor-1 [25], tenascin-C [26], n-terminal pro-brain natriuretic peptide [27–33], circulating endothelial glycocalyx components [26], lymphocyte hydrogen sulfide production [28], to mention a few. Different from these studies, we included results from clinical blood examinations as potential risk factors, which could be easier and faster to be assessed in the clinical practice. Furthermore, extracoronary echocardiographic findings and Z-values were also found to have predictive value for CAL [28, 33, 34]. Compared to those studies, investigation on blood-based biomarkers avoided the influence of variance in equipment and technicians.

In our study, lower albumin level was found to be a risk factor of CAL. Serum albumin is commonly used as a parameter to negatively indicate the activity of inflammatory as an acute phase reactant [35]. Hypoalbuminemia in KD patients was reported to be caused by vascular leakage, which was due to the elevation of vascular endothelial growth factor. Studies have found that vascular endothelial growth factor and its receptors (Fms-related tyrosine kinase-1 and kinase insert domain receptor) were involved in the development and progression of CAL in KD patients [36–38].

Although IVIG combined with aspirin were commonly adopted as the mainstay of initial treatment which could effectively decrease the development of CAL in KD patients, the high incidence of IVIG-resistant were reported in recent years [39–43]. Approximately 10–20% of pediatric patients with KD were reported to have persistent or recrudescence fever after the initial IVIG therapy [44, 45]. Patients that were not responsive to IVIG therapy were considered as at higher risk of incidence for CAL [40, 43]. Several studies suggested potential underlying mechanism that could partially explain the phenomenon. For example, through genome-wide association studies (GWAS), a number of genetic markers associated with both IVIG resistance and CAL formation were found in KD patients, including *inositol 1,4,5-trisphosphate 3-kinase C (ITPKC)*, *caspase-3 (CASP3)*, *FCGR2A*, *CD40*, and *interleukin 1 beta (IL-1B)* [46, 47]. Wang et al. found that the change of serum levels of IL-10 varied between patients with and without IVIG resistance after the usage of the medication, and the genetic polymorphisms of IL-10 were correlated to CAL [48]. However, in our study, IVIG resistance was not found to be associated with CAL. The potential reasons could be as followed. The IVIG resistance may suggest the severity of ongoing inflammation, nevertheless development of CAL might also be affected by other factors such as hemodynamics [49], of which the data were not collected in our study. Moreover, in the sensitivity analysis that involved IVIG resistance, even though the responsiveness of IVIG was not found to be associated with CAL directly, some of the other risk factors such as WBC and time of initial use of IVIG became nonsignificant after the addition of IVIG resistance. The mechanisms that lead to the variation should be investigated in future research.

It is crucial to identify the patients with elevated risk of CAL at early stage of the disease, through surveillance on specific risk factors in KD patients. Our study suggested several risk factors including age, gender and albumin, with

might be useful in clinical practice because these factors are easy to be measured and are possible to be tested frequently. It could help the pediatrician identify patients that might at high risk of CAL at early stage of the disease, for example upon admission to the hospital. Meanwhile, our findings could offer the pediatrician guidance on monitoring and providing targeted preventive and therapeutic measures. It could be inferred that patients with KD could be benefited from the timely medical treatment.

Strength and limitations

Our present study provided evidence on the associations between clinical biomarkers and the incidence of several CALs. There are a plenty of strengths that made our study valuable and practical. First, although the study was retrospective, we used data from medical records, which were obtained during the hospitalization. The accuracy and reliability of the data largely reduced the potential recall bias. Second, by including a group of clinical biomarkers as potential risk factors, combined with a comprehensive involvement of three major outcomes, our study provided an overall insight of the topic. Third, KD has been more prevalent in Asia area. Our study was carried out in Asian population (Chinese), which made our result proper to be generalized in the high-risk area of Asia. Forth, we investigated clinical characteristics and biomarkers that are easy to be examined, which made our conclusion more practical to be verified in future clinical research, and hence, to be implemented in clinics. However, there are several limitations of our study. First, the duration of follow-up was short. KD could have a life-long influence on the patients' health conditions. As reported by a Canadian study, 5% myocardial infarction patients less than 40 years old who underwent coronary angiography had lesions that were linked to sequelae of KD [50]. Therefore, it is necessary to follow up the participants as long as possible, to investigate the longitudinal risk factors for CAL. Second, the sample size of our study was relevant small. Due to the low incidence of KD in Guangdong province (approximately 5 per 100000) [7], it might be greatly time-consuming to recruit a large sample, even in multi-center research. Because of the insufficient sample, we cannot compare our findings between IVIG responsive and nonresponsive patients. The small sample size weakened the robustness of our conclusion. Third, information on some of the potential confounders that could have influence on the result were not collected in our study. The factors included family history, diet, sleep and other life-style factors, genetic data, etc. These data could not be implemented due to the retrospective feature of the study. Forth, we did not include patients in the recurrent episode. However, Nakamura et al. reported a higher risk of developing coronary artery sequelae with the recurrent episode [12]. This characteristic of our sample limited the generalization of our conclusion.

Conclusion

Our study analyzed data from a Chinese pediatric population with KD, and found that younger in age, male, lower serum albumin lever, and later initial use of IVIG were risk factors of CAL in this population. Our findings had high practicability to be implemented in clinical practice, however, future prospective multi-center studies, with longer follow-up duration, and involving more comprehensive exposure factors are essential to further verify our conclusion.

Declarations

Ethics approval and consent to participate

The protocol of the present study was reviewed and approved by the Guangzhou Women and Children Medical Center Ethics Committee (2021241A01) and was conducted according to the International Ethical Guidelines for Research Involving Human Subjects stated in the Declaration of Helsinki. The children's families provide written informed consent.

Consent for publication

Our manuscript does not contain information or images that could lead to identification of a study participant.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to the requirements of the hospital, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contribution

Conception and design: XY, XC; Data collection: XY, JD, YW; Analysis and interpretation of data: XY, ZL; Writing the manuscript and preparing tables: XY, XC; Critical revision of the manuscript: XY, XC, JD; Administrative, technical, or material support: XY, XC, YW; Obtaining funding: XY, XC; Supervision: XC; Review of the manuscript: all authors.

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