Analysis of Risk Factors of Kawasaki Disease With Coronary Artery Lesions

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Research Article

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Abstract

Objective:

To identify factors predictive of coronary artery lesions (CALs) in children with Kawasaki disease (KD).

Methods:

The clinical data of 420 children with KD who were hospitalized between January 2018 and December 2020 were retrospectively evaluated after assignment to groups by the presence of coronary artery aneurysm (CAA), coronary artery dilation (CAD), or no CALs. The association between coronary artery damage and patient clinical and laboratory values was investigated by pairwise comparison of the three groups. Univariate and multivariate logistic regression identified independent risk factors. The predictive value of patient variables for development of CAA and CAD was estimated by receiver operating characteristic curve analysis.

Results:

CALs occurred in 17.6% (94/420) of children with KD. Duration of fever, cervical lymphadenopathy, intravenous immune globulin resistance, immunoglobulin (Ig)A, procalcitonin, hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-reactive protein, and others differed between patients with CALs and without CALs and were significantly associated with the development of CAA and CAD. The largest area under the curve was for combined CAA or CAD indicators, 0.851 for CAA (sensitivity of 68.09% and specificity of 60.62%) and 0.714 for CAD (sensitivity of 65.96% and specificity of 70.77%). Fever of >7 days before treatment was predictive of severe CAA or CAD.

Conclusion:

Fever duration, ESR, IgA, Hb, and cervical lymphadenopathy were independent risk factors of CAA; CRP, ESR, and cervical lymphadenopathy were independent risk factors of CAD, with combined factors having increased sensitivity and specificity. Early, active treatment is essential to reduce the occurrence of CALs.

Introduction

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, is a self-limiting, acute disease characterized by fever, rash, and vasculitis. It is the most common cause of acquired coronary disease in the pediatric population. It is a systemic vascular disease that most often occurs in children 5 years of age and younger. The average age at diagnosis is 2 years. Coronary artery lesions (CALs) including luminal dilatations and aneurysms are the most significant long-term complication of KD and can occur in 15–25% of untreated KD patients[1–3]. Aneurysm formation can involve the coronary artery in up to 40% of patients and range from transient, mild dilatation or ectasia to giant coronary artery aneurysms (GCAAs). Patients with GCAAs are especially at risk for cardiac events including coronary artery thrombosis or stenosis, myocardial infarction, arrhythmias, or death[4]. Effective prevention and treatment

of CALs, associated with KD is a priority. In this analysis, children with KD were grouped by to the status of coronary artery injury and compared to identify the factors associated with the risk of CALs.

Methods

Patients:

This retrospective study included 420 children diagnosed with KD and hospitalized in the department of Pediatrics, Shengjing Hospital of China Medical University between January, 2018 and December, 2020. The children were assigned to three study groups. Group A included those with KD complicated by coronary artery aneurysm (CAA). Group B included those with KD complicated by coronary artery dilation (CAD), and group C included KD without CALs (NCALs). The diagnosis of KD was based on criteria established by the Japanese Kawasaki Disease Research Committee and the American Heart Association (AHA). The criteria included fever of > 38°C lasting at least 5 days without any other explanation and at least four of the following: polymorphous exanthema (a rash of any kind), bilateral bulbar conjunctival injection without exudates, erythema of the oral mucosa including the lips, pharynx, or tongue, peripheral extremity changes including erythema of palms or soles and/or swelling of the hands or feet, and unilateral cervical lymphadenopathy larger than 1.5 cm in diameter[2]. The diagnosis in patients with fevers of ≥ 5 days duration with fewer than four characteristic manifestations was incomplete KD.[2] An incomplete clinical diagnosis of KD can be made in patients with coronary artery disease detected by echocardiography[2]. The diagnoses were confirmed by more than two pediatric cardiologist; other possible diseases were excluded. Patients with incomplete clinical data, presenting with other febrile and exanthematous diseases, such as sepsis, toxic shock syndrome caused by scarlet fever, allergic and rheumatic diseases, and those who were previously found to have congenital heart disease by echocardiography were excluded.

Color Doppler ultrasonography was performed with GE VIVID E9 and Philips iE33 imaging systems and M5S, X5, and S8 probes. The probe frequencies were 1–5 and 2–8 MHz. Children were asleep or in a quiet state in the supine or left decubitus position. Standard sections of the heart were explored at the xiphoid process, apex, parasternal, and suprasternal fossa to explore. We evaluated the maximal internal diameters of the right coronary artery (RCA), the left coronary artery (LCA), left anterior descending artery (LADA), and left circumflex coronary artery (LCxA). Patient coronary artery Z-scores were classified as normal (< 2.5 standard deviations from the mean, normalized for body surface area), dilated (≥ 2.5 to < 4 standard deviations), aneurysmal (≥ 4 standard deviations), or giant aneurysm (> 10 standard deviations) of the maximal internal diameter at the base of the RCA or LADA. This study was approved by the ethics committee of China Medical University.

Clinical examination

Whole blood, plasma and serum samples were collected from patients with acute KD before any treatment with intravenous immune globulin (IVIG). Patient data included white blood cell (WBC) and

platelet (PLT) counts, hemoglobin (Hb), neutrophil percentage (N%), eosinophil percentage (E%), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IVIG resistance, brain natriuretic peptide (NT-proBNP), procalcitonin (PCT), interleukin (IL)-6, serum albumin (ALB), albumen/globulin ratio (A/G), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), fibrinogen (FIB), fibrinogen degradation products (FDP), D-dimer (DD), immunoglobulin (Ig)G, IgM, IgA, Na^+, and K^+.

Statistical analysis

The statistical analysis of CAL risk was performed with SPSS 23.0 statistical software. Quantitative data were reported as means ± standard deviation, qualitative data were reported as numbers (n) and percentages (%). Quantitative outcome measures were compared by the *t*-test if the distribution met normality criteria, or by the Mann-Whitney test if the data were not normally distributed. Comparison of the two qualitative outcome measures were done with the chi-square (χ^2) test. The three groups were compared in pairs. Univariate logistic regression was significant for variables included in multivariate logistic regression. The logistic regression analysis was conducted to evaluate the potential risk factors for CALs, and the predictive value of each risk factor was estimated by receiver operating curve (ROC) characteristic analysis. *P*-value of < 0.05 was considered statistically significant.

Results

Of the 420 patients included in this analysis, 261 (62.1%) were boys and 159 (37.9%) were girls. The male-to-female ratio was 1.6 : 1 with a mean age of 2.4 years (range 2 months to 11 years). CALs occurred in 17.6% (94/420) of infants with KD. Forty-seven children had CAAs in a total of 85 arteries, and the incidence by location was 37 of 85 (43%) in the RCA trunk followed by 30 of 85 (34.9%) the LCA trunk. The LCxA had the lowest incidence (3 of 85, 3.5%). Differences in duration of fever, Hb, ESR, gamma glutamyl transferase (GGT), IgA, FIB, conjunctival congestion, oral change, and cervical lymphadenopathy between group A (CAA) and group C (NCAL) were significant (all $p < 0.05$). Differences in age, Hb, ESR, lactate dehydrogenase (LDH), GGT, ALB, FDP, cervical lymphadenopathy, and IVIG resistance between group B (CAD) and group C (NCAL) were significant (all $p < 0.05$). Differences in duration of fever and PCT between group A and group B were significant (all $p < 0.05$, Table 1).

Table 1
Characteristics of patients in the three study groups during their acute KD phase

Variable	Group A (n = 47)	Group B (n = 47)	Group C (n = 326)	*P*
Sex				0.171
Male (%)	34 (72.3%)	32 (68.1%)	195 (59.8%)	
Female (%)	13 (27.7%)	15 (31.9%)	131 (40.2%)	
Classification				0.315
Complete KD	41 (87.2%)	43 (91.5%)	272 (83.4%)	
Incomplete KD	6 (12.8%)	4 (8.5%)	54 (16.6%)	
Conjunctival congestion	29 (61.7%)	39 (83.0%)	285 (87.4%)	< 0.001[b]
Oral change	34 (72.3%)	40 (85.1%)	296 (90.8%)	0.001[b]
Rash	26 (55.3%)	32 (68.1%)	222 (68.3%)	0.206
Edema of the hands and feet	24 (51.1%)	23 (48.9%)	213 (65.3%)	0.026
Cervical lymphadenopathy	31 (66.0%)	35 (74.5%)	306 (93.9%)	< 0.001[bc]
Crissum flush desquamation	10 (21.3%)	14 (29.8%)	107 (32.8%)	0.273
IVIG resistance	38 (10.3%)	36 (9.7%)	296 (80.0%)	0.005[c]
Age (months)	22.00 (8.00–48.00)	18.00 (7.00–28.00)	24.00 (14.00–36.00)	0.034[c]
Duration of fever	9.00 (6.00–14.00)	6.00 (5.00–7.00)	6.00 (5.00–7.00)	< 0.001[ab]
WBC	11.50 (7.76–13.11)	10.00 (7.90-13.67)	11.70 (8.02–15.99)	0.497
Hb	105.00(89.00-114.00)	105.00 (93.00-113.00)	108.00 (103.00-116.00)	0.001 [bc]
N	5.60 (2.40–10.10)	5.50 (3.10-9.00)	7.00 (3.20–9.68)	0.532

Group A, KD with coronary artery aneurysm; group B, KD with coronary artery dilation; group C, KD with no coronary artery lesions.

[a]Group A vs. Group B, [b]Group A vs. Group C, [c]Group B vs. Group C

Variable	Group A (n = 47)	Group B (n = 47)	Group C (n = 326)	*P*
PLT	390.00(232.00-527.00)	412.00(302.00-496.00)	370.50(283.50–547.00)	0.683
L	3.60 (2.20–5.30)	3.20 (2.00-4.60)	3.10 (2.10–4.50)	0.359
NLR	1.48 (0.65–2.79)	1.66 (0.79-3.00)	1.91 (0.84–3.91)	0.250
PLR	112.73 (73.33-174.14)	117.17 (73.26-171.67)	118.11 (82.69-165.76)	0.857
N%	49.30 (32.10–63.90)	53.60 (37.20–65.20)	58.35 (37.05–72.76)	0.094
E%	2.70 (0.90–5.90)	5.70 (1.90–7.92)	2.45 (0.90–4.30)	0.748
CRP	52.30 (10.10–103.00)	75.00 (32.00-103.00)	51.30 (16.93–92.90)	0.068
ESR	64.00 (33.00–81.00)	59.00 (35.00–77.00)	72.00 (54.00–88.00)	0.001[bc]
AST	25.00 (18.00–44.00)	25.00 (19.00–28.00)	24.00 (18.00-32.75)	0.657
ALT	21.00 (11.00–37.00)	25.00 (14.00–54.00)	20.00 (12.00–52.00)	0.616
LDH	262.00 (219.00-329.00)	281.00 (227.00-354.00)	256.50 (222.00-295.00)	0.046[c]
GGT	38.00 (21.00-102.00)	48.00(16.00–88.00)	22.00 (13.00-65.50)	0.009 [bc]
TB	5.00 (3.40-7.00)	4.70 (3.00-6.50)	3.80 (2.70–6.18)	0.060
TBA	5.90 (3.80–10.60)	6.40 (3.70–13.20)	5.50 (3.30–11.80)	0.471
ALB	31.30 (28.10–35.20)	31.60 (28.60–34.30)	32.60 (30.20–35.60)	0.042 [c]
A/G	0.80 (0.60–1.30)	0.80 (0.70–1.10)	0.80 (0.70-1.00)	0.482
Na	135.00 (133.00-138.00)	136.00 (134.00-138.00)	136.00 (134.00-138.00)	0.405
K	4.41 (4.09–4.80)	4.50 (3.66–4.78)	4.27 (3.92–4.70)	0.195

Group A, KD with coronary artery aneurysm; group B, KD with coronary artery dilation; group C, KD with no coronary artery lesions.

[a]Group A vs. Group B, [b]Group A vs. Group C, [c]Group B vs. Group C

Variable	Group A (n = 47)	Group B (n = 47)	Group C (n = 326)	*P*
IgG	16.00 (7.21–24.40)	17.20 (8.31–21.70)	18.70 (6.89–22.40)	0.723
IgM	1.28 (0.72–1.67)	0.90 (0.67–1.25)	0.99 (0.72–1.30)	0.062
IgA	0.79 (0.48–1.41)	0.55 (0.43–1.05)	0.61 (0.43–0.98)	0.035[b]
PT	13.30 (12.30–14.30)	12.80 (12.20–13.80)	13.00 (12.10–14.00)	0.297
FIB	3.80 (2.60–5.20)	4.30 (3.90–4.80)	4.50 (3.90-5.00)	0.043[b]
FDP	5.30 (2.20–11.60)	5.60 (3.10–9.60)	4.10 (2.80–6.60)	0.042 [c]
DD	523.00(258.00-1260.00)	595.00(344.00-1046.00)	450.50(272.00-729.50)	0.078
PCT	0.17 (0.13–0.59)	0.63 (0.28–1.27)	0.37 (0.17-1.00)	0.009[a]
proBNP	373.70(156.20–1587.00)	646.20(268.60–2068.00)	449.25(167.70-1041.50)	0.104
IL6	38.49 (28.21–201.50)	89.54 (47.75–191.70)	66.26 (22.88-154.88)	0.074
VD	42.51 (32.23–45.89)	32.40 (26.19–39.24)	33.61 (23.31–46.14)	0.051
Group A, KD with coronary artery aneurysm; group B, KD with coronary artery dilation; group C, KD with no coronary artery lesions.				
[a]Group A vs. Group B, [b]Group A vs. Group C, [c]Group B vs. Group C				

Multivariate logistic regression included the variables that were significantly associated with CALs in the univariate logistic regression analysis. The results in group A and group C are shown in Table 2.1. Multivariate logistic regression showed that the duration of fever, Hb, ESR, IgA and cervical lymphadenopathy were significantly associated with CAA in this group of children with KD ($p < 0.05$). ROC curve analysis found that the area under the curve (AUC) of any of the five variables as a single index was not high, but that it increased with combination of the five. The AUC was the largest (0.851) when the five indicators were combined (Table 2.2 and Fig. 1).

Table 2.1
Logistic regression analysis including group A (coronary artery aneurysms) and group C (no coronary artery lesions)

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR	P	OR	P
Sex	0.569 (0.289–1.119)	0.102		
Classification	0.737 (0.298–1.822)	0.509		
Conjunctival congestion	0.232 (0.118–0.454)	< 0.001		
Oral change	0.265 (0.126–0.556)	< 0.001		
Rush	0.574 (0.309–1.069)	0.080		
Edema of the hands and feet	0.554 (0.299–1.025)	0.060		
Cervical lymphadenopathy	0.127 (0.060–0.269)	< 0.001	0.163 (0.060–0.442)	< 0.001
Crissum flush desquamation	0.553 (0.265–1.155)	0.115		
IVIG resistance	0.428 (0.189–0.970)	0.042		
Age(months)	1.000 (0.986–1.014)	0.999		
Duration of fever	1.349 (1.223–1.488)	< 0.001	1.290 (1.149–1.449)	< 0.001
WBC	0.999 (0.989–1.008)	0.816		
HB	0.954 (0.930 – 0.919)	< 0.001	0.963 (0.932–0.995)	0.026
N	0.987 (0.931–1.046)	0.650		
PLT	1.001 (0.999–1.003)	0.334		
L	1.162 (1.014–1.331)	0.031		
NLR	0.962 (0881 – 1.050)	0.381		
PLR	0.998 (0.995–1.002)	0.361		
N%	0.987(0.974–1.001)	0.060		
E%	1.070 (0.964–1.188)	0.206		
CRP	1.001 (0.996–1.006)	0.685		
ESR	0.984 (0.972–0.995)	0.005	0.982 (0.966–0.998)	0.030
AST	0.999 (0.992–1.006)	0.686		
ALT	0.992 (0.984–1.001)	0.071		
LDH	1.002 (0.999–1.005)	0.229		

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR	P	OR	P
GGT	1.002 (0.998–1.005)	0.302		
TB	1.015 (0.988–1.043)	0.277		
TBA	0.999 (0.991–1.007)	0.750		
ALB	0.943 (0.878–1.013)	0.108		
A/G	1.113 (0.474–2.612)	0.806		
Na	0.899 (0.812–0.994)	0.038	0.982 (0.966–0.998)	0.030
K	1.435 (0.846–2.435)	0.181		
IgG	0.993 (0.965–1.022)	0.643		
IgM	1.918 (1.073–3.428)	0.028		
IgA	2.245 (1.401-3.600)	0.001	2.471 (1.359–4.492)	0.003
PT	1.176 (1.045–1.322)	0.007		
FIB	0.631 (0.475–0.839)	0.002		
FDP	1.016 (0.995–1.039)	0.140		
DD	1.000 (1.000–1.000)	0.280		
PCT	1.057 (0.982–1.138)	0.141		
proBNP	1.000 (1.000–1.000)	0.112		
IL6	1.001 (1.000-1.002)	0.125		
VD	1.015 (0.994–1.036)	0.158		

Table 2.2
Receiver operating characteristic area under the curve (AUC) analysis of the sensitivity and specificity of single and combined indexes to predict coronary artery aneurysms

Variable	Cutoff	AUC	95% CI	*P*	Sensitivity	Specificity
Duration of fever	9	0.732	0.634–0.830	< 0.001	55.32%	88.62%
Hb	145.00	0.632	0.534–0.760	0.003	2.13%	100.00%
ESR	-	0.615	0.534–0.696	0.041	-	-
IgA	0.72	0.618	0.524–0.711	0.009	68.09%	60.74%
Cervical lymphadenopathy	-	0.639	0.544–0.735	0.002	-	-
Fever + Hb + cervical lymph	0.1324[a]	0.826	0.757–0.894	< 0.001	74.47%	84.31%
Fever + ESR + cervical lymph	0.1524[b]	0.806	0.726–0.886	< 0.001	72.34%	87.08%
Fever + IgA + cervical lymph	0.1478[c]	0.817	0.736–0.898	< 0.001	74.47%	84.62%
Fever + Hb + ESR + IgA + cervical lymph	0.7235[d]	0.851	0.789–0.914	< 0.001	68.09%	60.62%

[a] $e^{X1x0.275-X2x0.039-X5x1.938+1.744}/1+e^{X1x0.275-X2x0.039-X5x1.938+1.744}$

[b] $e^{X1x0.274-X3x0.011-X5x1.8-1.788}/1+e^{X1x0.274-X3x0.011-X5x1.8-1.788}$

[c] $e^{X1x0.276+X4x0.818-X5x2.109-2.991}/1+e^{X1x0.276+X4x0.818-X5x2.109-2.991}$

[d] $e^{X1x0.261-X2x0.046-X3x0.013+X4x0.901-X5x1.965+2.676}/1+e^{X1x0.261-X2x0.046-X3x0.013+X4x0.901-X5x1.965+2.676}$

Presence or absence of CAD was a dependent variable, and the indicators of statistical significance in the univariate analysis were independent variables included in the multivariate logistic regression analysis. The results for group B and group C in Table 3.1. show that CRP, ESR, and cervical lymphadenopathy were independent risk factors of CAD. The AUC was the largest for the combination of CRP, ESR, and cervical lymphadenopathy, indicating that its diagnostic performance was optimal (Table 3.2. and Fig. 2).

Table 3.1
Logistic regression analysis including group B (coronary artery dilation) and group C (no coronary artery lesions)

Variables	Univariate logistic regression		Multivariate logistic regression	
	Odds Ratio	*P*	Odds Ratio	*P*
Sex	0.698 (0.364–1.339)	0.279		
Classification	0.469 (0.161–1.360)	0.163		
Conjunctival congestion	0.701 (0.306–1.605)	0.40		
Oral change	0.579 (0.239–1.405)	0.227		
Rush	0.990 (0.513–1.908)	0.976		
Edema of the hands and feet	0.508 (0.275–0.941)	0.031	0.439 (0.216–0.895)	0.023
Cervical lymphadenopathy	0.191 (0.086–0.423)	< 0.001	0.291 (0.114–0.741)	0.010
Crissum flush desquamation	0.868 (0.446–1.691)	0.678		
IVIG resistance	0.332 (0.153–0.718)	0.005		
Age (months)	0.975 (0.954–0.995)	0.016		
Duration of fever	1.002 (0.883–1.137)	0.976		
WBC	0.980 (0.927–1.036)	0.485		
HB	0.956 (0.930–0.983)	0.001		
N	0.983 (0.926–1.044)	0.585		
PLT	1.000 (0.998–1.003)	0.647		
L	1.037 (0.886–1.213)	0.650		
NLR	0.969 (0.891–1.055)	0.469		
PLR	1.000 (0.996–1.003)	0.758		
N%	0.993 (0.979–1.006)	0.290		
E%	1.013 (0.905–1.134)	0.826		
CRP	1.006 (1.001–1.010)	0.016	1.006 (1.000-1.012)	0.034
ESR	0.982 (0.971–0.994)	0.002	0.983 (0.971–0.996)	0.011
AST	0.989 (0.974–1.005)	0.173		
ALT	0.997 (0.992–1.003)	0.298		
LDH	1.003 (1.000-1.006)	0.054		

Variables	Univariate logistic regression		Multivariate logistic regression	
	Odds Ratio	*P*	Odds Ratio	*P*
GGT	1.002 (0.998–1.005)	0.298		
TB	1.003 (0.969–1.039)	0.853		
TBA	1.001 (0.996–1.007)	0.608		
ALB	0.944 (0.878–1.015)	0.122		
A/G	1.759 (0.798–3.881)	0.162		
Na	0.974 (0.868–1.092)	0.646		
K	1.145 (0.686–1.911)	0.604		
IgG	0.998 (0.970–1.028)	0.916		
IgM	0.952 (0.515–1.760)	0.875		
IgA	1.031 (0.728–1.460)	0.864		
PT	0.940 (0.762–1.159)	0.562		
FIB	0.989 (0.717–1.365)	0.948		
FDP	1.017 (0.996–1.038)	0.110		
DD	1.000 (1.000–1.000)	0.166		
PCT	1.097 (0.937–1.284)	0.250		
proBNP	1.000 (1.000–1.000)	0.767		
IL6	1.002 (1.000-1.003)	0.035		
VD	0.987 (0.965–1.008)	0.221		

Table 3.2
Receiver operating characteristic area under the curve (AUC) analysis of the sensitivity and specificity of single and combined indexes to predict coronary artery dilation

Variable	Cutoff	AUC	95% CI	*P*	Sensitivity	Specificity
CRP	69.85	0.605	0.521–0.689	0.019	61.70%	59.08%
ESR	3.50	0.632	0.541–0.724	0.003	100%	0.31%
Cervical lymphadenopathy	-	0.597	0.502–0.692	0.032	-	-
CRP + cervical[a]	0.1787[a]	0.679	0.595–0.764	0.043	40.43%	88.31%
ESR + cervical[b]	0.1254[b]	0.654	0.560–0.748	0.048	53.19%	76.31%
CRP + ESR + cervical[c]	0.1373[c]	0.703	0.615–0.792	0.045	57.45%	80.92%
[a] $e^{X1x0.007-X3x1.784-0.909}/1+e^{X1x0.007-X3x1.784-0.909}$						
[b] $e^{-0.014xX2-X3x1.407+0.154}/1+e^{-0.014xX2-X3x1.407+0.154}$						
[c] $e^{X1x0.008-X2x0.017-X3x1.486-0.144}/1+e^{X1x0.008-X2x0.017-X3x1.486-0.144}$						

The comparison results between group A and group B were shown as Table 4.1, and the ROC curve was drawn to evaluate its predicted value (Table 4.2 and Fig. 3).

Table 4.1
Logistic regression analysis including group A (coronary artery aneurysm) and group B (coronary artery dilation)

Variables	Univariate logistic regression		Multivariate logistic regression	
	Odds Ratio	*P*	Odds Ratio	*P*
Sex	0.816 (0.336–1.978)	0.652		
Classification	1.573 (0.414–5.981)	0.506		
Conjunctival congestion	0.330 (0.126–0.864)	0.024		
Oral change	0.458 (0.164–1.277)	0.136		
Rush	0.580 (0.250–1.345)	0.205		
Edema of the hands and feet	1.089 (0.485–2.445)	0.837		
Cervical lymphadenopathy	0.664 (0.273–1.619)	0.368		
Crissum flush desquamation	0.637 (0.249–1.627)	0.346		
IVIG resistance	1.290 (0.478–3.479)	0.615		
Age(months)	1.018 (0.997–1.038)	0.094		
Duration of fever	1.294 (1.129–1.484)	< 0.001	1.285 (1.111–1.487)	0.001
WBC	1.032 (0.974–1.094)	0.280		
HB	0.995 (0.968–1.023)	0.731		
N	1.002 (0.934–1.075)	0.952		
PLT	1.000 (0.998–1.003)	0.742		
L	1.109 (0.927–1.327)	0.258		
NLR	0.992 (0.888–1.108)	0.885		
PLR	0.999 (0.994–1.003)	0.567		
N%	0.994 (0.976–1.013)	0.522		
E%	1.052 (0.918–1.205)	0.469		
CRP	0.995 (0.989–1.002)	0.158	1.006 (1.000-1.012)	0.034
ESR	1.002 (0.987–1.016)	0.841	0.983 (0.971–0.996)	0.011
AST	1.021 (0.997–1.045)	0.083		
ALT	0.988 (0.974–1.003)	0.110		
LDH	0.999 (0.994–1.003)	0.566		

Variables	Univariate logistic regression		Multivariate logistic regression	
	Odds Ratio	*P*	Odds Ratio	*P*
GGT	1.000 (0.994–1.006)	0.995		
TB	1.011 (0.973–1.051)	0.580		
TBA	0.997 (0.988–1.006)	0.548		
ALB	0.998 (0.921–1.082)	0.962		
A/G	0.733 (0.300–1.790)	0.496		
Na	0.939 (0.830–1.061)	0.311		
K	1.181 (0.641–2.175)	0.593		
IgG	0.995 (0.959–1.033)	0.789		
IgM	1.690 (0.821–3.480)	0.154		
IgA	0.990 (0.955–1.025)	0.562		
PT	1.226 (0.934–1.609)	0.142		
FIB	0.742 (0.538–1.021)	0.067		
FDP	0.998 (0.969–1.028)	0.903		
DD	1.000 (1.000–1.000)	0.765		
PCT	1.025 (0.949–1.108)	0.523		
proBNP	1.000 (1.000–1.000)	0.389		
IL6	1.000 (0.999–1.001)	0.541		
VD	1.041 (1.006–1.078)	0.023		

Table 4.2
Receiver operating characteristic area under the curve (AUC) analysis of the sensitivity and specificity of the duration of fever

Variable	Cutoff	AUC	95%CI	*P*	Sensitivity	Specificity
Duration of fever	7	0.732	0.626–0.838	< 0.001	74.47%	70.21%

Discussion

KD is an acute systemic inflammatory syndrome involving medium and small blood vessels commonly and occurring in children under 5 years of age. CALs caused by KD have become the most common acquired heart disease in children and may be a risk factor for ischemic heart disease in adults. In this study, the incidence of CALs was 17.6%. CAA was most frequent in the RCA trunk (37/85, 43%), followed

by the LCA trunk (30/85, 34.9%), The lowest incidence was in the LCxA (3/85, 3.5%). Coronary arteritis is first seen 6 to 8 days after the onset of disease. Beginning on day 10, the arterial walls are infiltrated by lymphocytes and macrophages, with damage of the internal elastic lamina and medial smooth muscle cells. Around day 12, aneurysms start to form, are considered to be related to coronary vasculitis and hypercoagulability, and reaching a peak diameter within 1 to 2 months. If the damage is severe, and thrombosis may occur as blood pools in the aneurysm[5].

The results obtained in several large samples and the 2017 AHA KD Guidelines[6], indicate that male sex, low blood sodium, high AST, high neutrophil and low PLT counts, heat duration ≥ 10 days, WBC > 20×10^9/L, increased ESR, decreased ALB, anemia, and incomplete KD are risk factors for CALs[7–8]. Previous studies have found that cytokines and inflammatory mediators interact to promote and amplify immune effects that lead to coronary artery injury. The ESR is consistently elevated during the acute phase of KD but may be unreliable as a marker of disease activity after the administration of IVIG[9–11]. CRP is known to have a significant association with disease severity and the development of CALs[9–10, 12]. The NLR and platelet/lymphocyte ratio calculated from the whole blood cell count are widely studied inflammatory indexes that are markers of the severity of cardiovascular and coronary artery disease in KD[13–14]. Recent studies have shown that an increased proportion of eosinophils and an increase in DD are associated with KD complicated by CALs. [15, 16] It is currently believed that KD is closely related to the high activation of the immune system, and. overactivation of lymphocytes in the acute phase promotes the proliferation and differentiation of B cells to produce a variety of autoantibodies and immunoglobulins. [17] At the same time, the overactivation of T cells results in secretion of a cascade of cytokines and inflammatory factors that damage vascular endothelial cells and cause late CAD and even CAAs. Therefore, IgA, IgM, and IgG were included in this analysis along with the clinical manifestations of KH. We found that the incidence of both CAA and CAD was relatively high in children with cervical lymphadenopathy and the differences were statistically significant. The reasons need further analysis after expanding the sample size. Multivariate logistic regression showed that the CAA group had significantly longer fever duration, higher ESR and IgA and lower Hb compared with the NCAL group. ROC curve analysis showed that there were limitations in the prognostic value of fever duration, ESR, IgA, Hb, and cervical lymphadenopathy alone. The AUC for the identifying patients at risk of CAA was the largest when the five factors were combined (0.851) and had a sensitivity of 68.09% and a specificity of 60.62%. The logistic regression equation was:

$$e^{X1x0.261-X2x0.046-X3x0.013+X4x0.901-X5x1.965+2.676}/1+e^{X1x0.261-X2x0.046-X3x0.013+X4x0.901-X5x1.965+2.676}.$$

The CAD group had significantly higher CRP and ESR than the NCAL group. The AUC was largest when CRP, ESR, and cervical lymphadenopathy were combined, and had a sensitivity of 57.45% and a specificity of 80.92%. the logistic regression equation was:

$$X1x0.008-X2x0.017-X3x1.486-0.144/1+e^{X1x0.008-X2x0.017-X3x1.486-0.144}.$$

According to current estimates, CAA develops in 15–25% of untreated KH patients and in 5% of treated patients. A long duration of fever indicates a strong and persistent inflammatory response, and a prolonged duration of coronary artery injury leads to an increased incidence of coronary artery disease. The most important factor protecting from complications is early initiation of immunoglobulin treatment within 7 to 10 days after symptom onset[18–21]. In our cohort, the number of febrile days before diagnosis and treatment was significantly longer in the CAA than in the CAD and NCAL groups(as shown inTable 1), which is consistent with previous studies.

Limitations

First, this was a retrospective study with a limited sample size and possible selection bias. Secondly, the study only considered the results of ultrasound of coronary arteries in the acute stage of KD and did not include follow-up data of the coronary arteries. In the future, the sample size should be expanded and follow-up data should be included to further validate the results.

Conclusions

In summary, fever duration, ESR, IgA, Hb and cervical lymphadenopathy were independent predictors of CAA in the acute phase of KD. Combination of the five indicators had the highest predictive value. Children with KD who have increased CRP, ESR and cervical lymphadenopathy before treatment had an increased risk of CAD. Careful attention should be paid to children with the above risk factors. Early and active treatment is essential to reduce the occurrence of CALs.

Declarations

Ethics approval and consent to participate: This study was approved and reviewed by the Ethics Committee of China Medical University.(2021PS537K). I**nformed consent** was obtained from all subjects or, if subjects are under 16, from a parent and/or legal guardian. And all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors have no financial conflict of interest to report.

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Figures

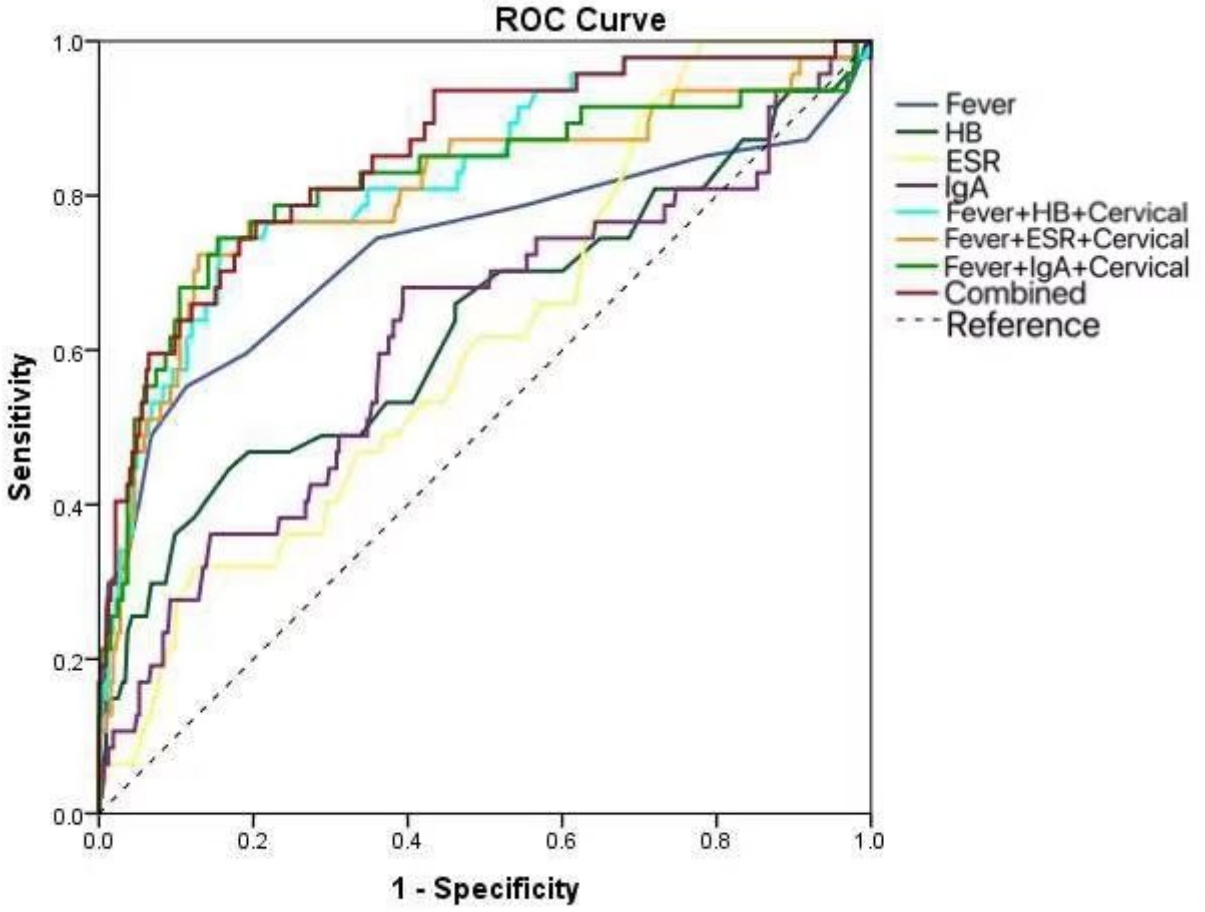

Figure 1

Receiver operating characteristic areas under the curve of coronary artery aneurysms and separate and joint consideration of risk factors.

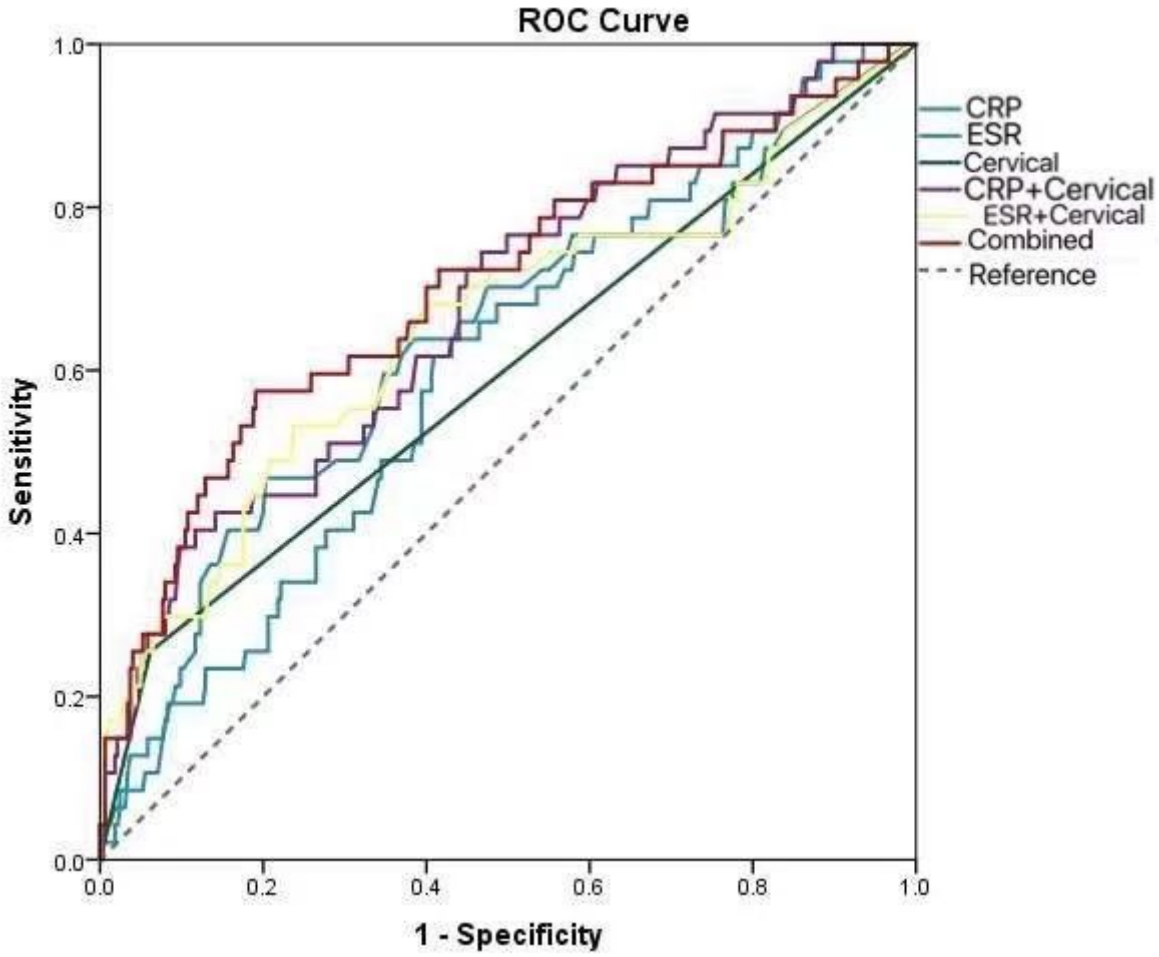

Figure 2

Receiver operating characteristic areas under the curve of coronary artery dilation and separate and joint consideration of risk factors.

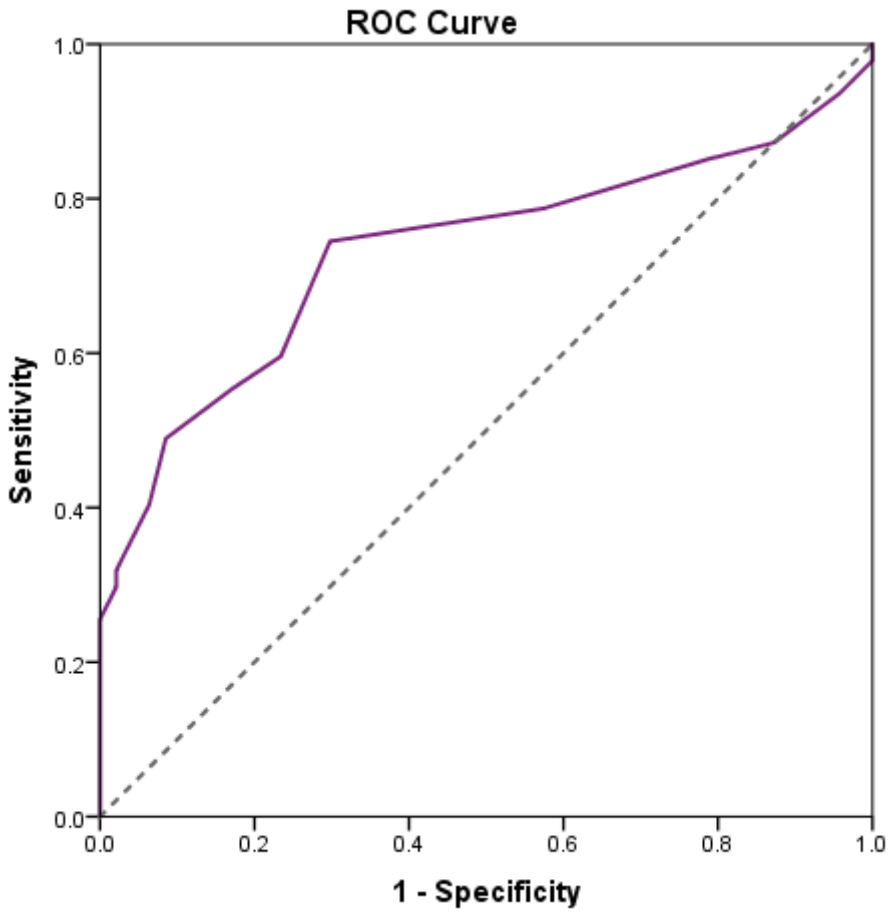

Figure 3

Receiver operating characteristic area under the curve for fever duration before IVIG.